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(54) Title: STABILIZED ORAL PHARMACEUTICAL COMPOSITION

(57) Abstract: An orally deliverable pharmaceutical composition is provided comprising an aminosulfonyl-comprising drug, for example a selective cyclooxygenase-2 inhibitory drug such as celecoxib, and a solvent liquid comprising a polyethylene glycol and one or more free radical-scavenging antioxidants. At least a substantial part of the drug is in dissolved form in the solvent liquid. The composition has rapid-onset properties and is useful in treatment of cyclooxygenase-2 mediated conditions and disorders.

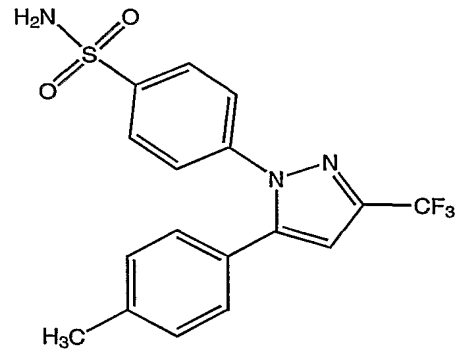
STABILIZED ORAL PHARMACEUTICAL COMPOSITION

FIELD OF THE INVENTION

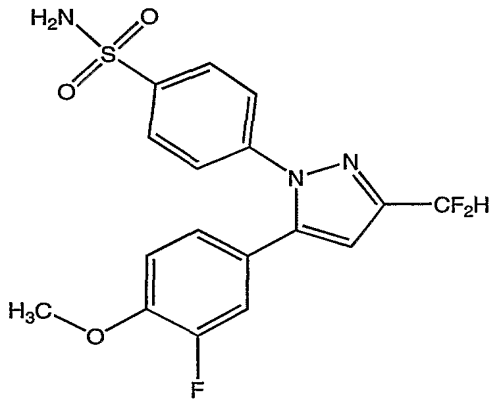
The present invention relates to orally deliverable pharmaceutical compositions that comprise a drug of low water solubility, more particularly to such compositions where the drug is in dissolved form.

BACKGROUND OF THE INVENTION

Several compounds having a molecular structure that comprises an aminosulfonyl functional group (herein referred to as aminosulfonyl-comprising compounds) have been reported as having therapeutically and/or prophylactically useful selective cyclooxygenase-2 (COX-2) inhibitory effects, and have been disclosed as having utility in treatment or prevention of specific COX-2 mediated disorders or of such disorders in general. Among such compounds are a large number of substituted pyrazolyl benzenesulfonamides as reported in U.S. Patent No. 5,760,068 to Talley *et al.*, including for example the compound 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, also referred to herein as celecoxib (I), and the compound 4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, also referred to herein as deracoxib (II).

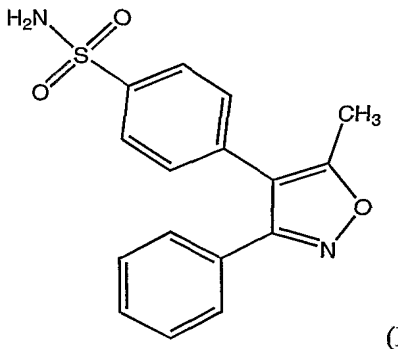


(I)



(II)

Other aminosulfonyl-comprising compounds reported to have therapeutically and/or prophylactically useful selective COX-2 inhibitory effect are substituted isoxazolyl benzenesulfonamides as reported in U.S. Patent No. 5,633,272 to Talley *et al.*, including the compound 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide, also referred to herein as valdecoxib (III).



(III)

A need for formulated compositions of selective COX-2 inhibitory drugs, particularly rapid-onset compositions of such drugs, exists. Rapid-onset drug delivery systems can provide many benefits over conventional dosage forms. Generally, rapid-onset preparations provide a more immediate therapeutic effect than standard dosage forms. For example, in the treatment of acute pain, for example in headache or migraine, rapid-onset dosage forms are useful to provide fast pain relief.

Australian Patent Applications No. 200042711, No. 200043730 and No. 200043736 disclose compositions comprising a selective COX-2 inhibitory drug, a $5HT_1$ receptor agonist and caffeine, said to be useful for treating migraine.

U.S. Patent No. 5,993,858 to Crison & Amidon discloses an excipient formulation for increasing bioavailability of a poorly water-soluble drug. The formulation is said to be self-microemulsifying and to comprise an oil or other lipid material, a surfactant and a hydrophilic co-surfactant. The choice of surfactant is said to be less critical than the choice of co-surfactant, which reportedly should have an HLB (hydrophilic-lipophilic balance) number greater than 8. A preferred example of such a co-surfactant is said to be Labrasol™ of Gattefossé, identified as a product "comprised of medium-chain triglycerides derived from coconut oil" having HLB of 14. A formulation prepared containing 15 mg nifedipine in a size 1 (0.5 ml) capsule, *i.e.*, at a concentration of 30 mg/ml, is described as a "clear solution" at 70°C but a "semi-solid" at room temperature.

Cited in above-referenced U.S. Patent No. 5,993,858 is prior work by Farah *et al.* in which a self-microemulsifying formulation was investigated for improving *in vitro* dissolution of indomethacin. The formulation of Farah *et al.* reportedly comprised an oil phase material Gelucire™ of Gattefossé, together with a polyethylene glycol capric/caprylic glyceride product having HLB of 10, a propylene

glycol laurate product having HLB of 4, and diethylene glycol monoethyl ether.

Drugs of low water solubility are sometimes orally administered in suspension in an imbibable aqueous liquid. For example, a suspension of particulate celecoxib in a vehicle of apple juice is disclosed in co-assigned International Patent Publication No. WO 00/32189, incorporated herein by reference. Also disclosed therein is a dilute solution of celecoxib in a mixture of PEG-400 (polyethylene glycol having an average molecular weight of about 400) and water in a 2:1 ratio by volume.

The suspension and solution compositions of WO 00/32189 are indicated therein to have comparable bioavailability. However, following oral administration to dogs, the time taken for blood serum celecoxib concentration to reach a maximum level (T_{max}) was shorter for the solution composition than for the suspension.

Above-cited U.S. Patent No. 5,760,068 discloses that its subject pyrazolyl benzenesulfonamide compounds, of which celecoxib and deracoxib are examples, can be administered parenterally as isotonic solutions in a range of solvents including polyethylene glycol and propylene glycol. It is also disclosed therein that the subject compounds can alternatively be present in a controlled-release capsule or tablet formulation for oral administration wherein, for example, such a compound is dispersed in hydroxypropylmethylcellulose (HPMC).

Above-cited U.S. Patent No. 5,633,272 discloses that its subject isoxazolyl benzenesulfonamides, of which valdecoxib is an example, can be administered parenterally as isotonic solutions in a range of solvents including polyethylene glycol and propylene glycol. It is also disclosed therein that the subject compounds can alternatively be present in a controlled-release capsule or tablet formulation for oral administration wherein, for example, such a compound is dispersed in HPMC.

It is known to encapsulate liquid formulations, for example in soft or hard gelatin capsules, to provide a discrete dosage form.

Many aminosulfonyl-comprising selective COX-2 inhibitory drugs, including celecoxib, deracoxib and valdecoxib, have low solubility in aqueous media. In addition, some, for example celecoxib, have relatively high dose requirements. These properties present practical problems in formulating concentrated solutions of such drugs for rapid-onset, oral administration. With respect to high dose, low solubility drugs, the size of the capsule or volume of solution required to provide a therapeutic

dose becomes a limiting factor. For example, a drug that has a solubility of 10 mg/ml in a given solvent and a therapeutic dose of 400 mg/day would require ingestion of 40 ml of solution. Such a volume can be inconvenient or unacceptable for consumption in imbibable form; this volume also presents particular problems where an encapsulated dosage form is desired because capsules that contain more than about 1.0 ml to about 1.5 ml of liquid are generally considered to be too large for comfortable swallowing. Thus, where such a solution is administered in capsule form, multiple capsules would need to be ingested in order to provide the required dose. To avoid such problems, a solvent must be selected wherein the drug has relatively high solubility.

Moreover, the solvent should be selected not to chemically interact with or degrade the drug. For solutions and/or suspensions that are to be encapsulated as oral dosage forms, the solvent must further be selected not to degrade, erode, or react with the capsule wall material. Further, liquids that can easily migrate through a capsule wall, *e.g.*, water in an amount greater than about 5% by weight of the solution, and low molecular weight water-soluble, volatile organic compounds such as alcohols, ketones, acids, amines and esters, are generally unsuitable for encapsulation.

Water-miscible, nonvolatile liquids such as polyethylene glycols have been successfully used in encapsulated solution formulations. Moreover, polyethylene glycols are also good solvents for drugs of low water solubility because they are known to improve aqueous drug solubility. For example, celecoxib, which has very low solubility in water, is highly soluble (>300 mg/g) in a 2:1 mixture of PEG-400 and water.

However, we have now discovered that polyethylene glycol, when used as a solvent for an aminosulfonyl-comprising drug such as celecoxib, can result in drug instability. This problem presents practical difficulties in forming a chemically stable solution of an aminosulfonyl-comprising drug using polyethylene glycol (which, as described above, can be otherwise advantageous) as a solvent.

As described hereinbelow, treatment with selective COX-2 inhibitory drugs of low water solubility is indicated in a very wide array of COX-2 mediated conditions and disorders, and several clinically important examples of such drugs comprise an aminosulfonyl functional group. Therefore, if the problem of chemical instability of

the drug in polyethylene glycol solution could be overcome, a significant advance would be realized in treatment of COX-2 mediated conditions and disorders, particularly in treatment of acute disorders where early relief from pain or other symptoms is desired. It would represent an especially important advance in the art to provide an effective method of treatment of acute pain, for example in headache or migraine, using a chemically stable solution of an aminosulfonyl-comprising selective COX-2 inhibitory drug having polyethylene glycol as a solvent, if such a solution could be prepared.

SUMMARY OF THE INVENTION

There is now provided an orally deliverable pharmaceutical composition comprising a drug of low water solubility and a solvent liquid that comprises at least one pharmaceutically acceptable polyethylene glycol and at least one pharmaceutically acceptable free radical-scavenging antioxidant, wherein a substantial portion, for example at least about 15% by weight, of the drug is in dissolved or solubilized form in the solvent liquid, and wherein the drug comprises an aminosulfonyl functional group and/or is capable of reacting with a polyethylene glycol or polyethylene glycol degradation product to form an addition compound.

The term "solvent liquid" herein encompasses all of the components of the liquid medium in which a particular drug is dissolved or solubilized including but not limited to one or more solvents, co-solvents, antioxidants, crystallization inhibitors, dispersants, surfactants, co-surfactants, sweeteners, flavoring agents, colorants, *etc.*

In a presently preferred composition of the invention, substantially all of the drug is in dissolved or solubilized form in the solvent liquid and substantially none of the drug is in solid particulate form. Such a composition is referred to herein as a "solution". It is particularly preferred that the solution is finely self-emulsifiable in simulated gastric fluid, as described hereinbelow.

An alternative composition of the invention comprises, in addition to a first portion of the drug in dissolved or solubilized form, a second portion of the drug in particulate form dispersed in the solvent liquid. In this embodiment, part of the drug is in solution and part is in suspension. Such a composition is referred to herein as a "solution/suspension".

In a presently preferred embodiment, the solution or solution/suspension is

encapsulated in one or more capsules that release the drug by capsule wall breakdown within a short period of time after entry into the gastrointestinal tract. In this embodiment, the capsule wall optionally comprises a cellulosic polymer component wherein hydroxyl groups are substituted by methoxyl and/or hydroxypropoxyl groups, for example HPMC.

Compositions of the invention have been found to resolve the problem of drug instability in a surprisingly effective manner. Thus, for the first time, a poorly water-soluble drug that comprises an aminosulfonyl functional group, and/or is capable of reacting with a polyethylene glycol or polyethylene glycol degradation product to form an addition compound, is presented in a stable, concentrated solution formulation having a polyethylene glycol as a solvent. Preferably such formulations are presented in a dose form that is convenient for oral administration. Formulations of the invention are particularly advantageous because they are chemically stable, permit a high concentration of the drug, are suitable for encapsulation, and, following oral administration thereof, can permit rapid absorption of the drug into the bloodstream thereby providing rapid onset of therapeutic action.

It can be theorized that a poorly water-soluble drug can provide more rapid onset of therapeutic effect when orally administered in solution, particularly a self-emulsifiable solution, than in particulate form because the process of dissolution in the gastrointestinal tract is not required. An even greater advantage by comparison with a solid formulation such as a tablet can be postulated because neither disintegration nor dissolution is required in the case of the solution composition.

Additionally, a drug administered in imbibable solution can be available for absorption higher in the alimentary tract, for example, in the mouth and esophagus, than one that becomes available for absorption only upon disintegration of the carrier formulation in the stomach or bowel.

A further advantage of liquid dosage forms such as imbibable solutions and solution/suspensions for many subjects is that these dosage forms are easy to swallow. A yet further advantage of imbibable liquid dosage forms is that metering of doses is continuously variable, providing infinite dose flexibility. The benefits of ease of swallowing and dose flexibility are particularly advantageous for infants, children and the elderly.

When encapsulated, a solution or solution/suspension can provide the subject with the beneficial rapid absorption characteristics associated with liquid formulations in addition to the convenience of a discrete, easy to swallow capsule form.

The highly concentrated solutions permitted by the present invention are beneficial for several reasons. First, concentrated solutions are less costly to package and easier to transport and handle than dilute solutions. Second, concentrated solutions provide flexibility in administration as they can be administered with any desired degree of dilution. And third, concentrated drug solutions, especially when encapsulated, do not require consumption of large volumes of fluid, which can be uncomfortable for many patient populations.

In one embodiment, a method of analgesia is provided comprising orally administering, to a subject in need of analgesia, an effective pain-relieving amount of an aminosulfonyl-comprising selective COX-2 inhibitory drug composition of the invention. In another embodiment, a method of treatment and/or prevention of headache or migraine is provided comprising orally administering, to a subject in need of such treatment or prevention, an aminosulfonyl-comprising selective COX-2 inhibitory drug composition of the invention and a vasomodulator, for example a methylxanthine, wherein the selective COX-2 inhibitory drug and the vasomodulator are administered in effective pain-relieving total and relative amounts. The selective COX-2 inhibitory drug and the vasomodulator can be administered as components of separate compositions or of a single composition. Such a single composition comprising (a) an aminosulfonyl-comprising selective COX-2 inhibitory drug, formulated as provided herein, and (b) a vasomodulator, is a further embodiment of the invention. A presently preferred methylxanthine is caffeine.

Other features of this invention will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION OF THE INVENTION

Novel pharmaceutical compositions according to the present invention comprise one or more orally deliverable dose units. The term "orally deliverable" herein means suitable for oral administration. The term "oral administration" herein includes any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject,

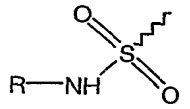
whether or not the agent or composition is swallowed. Thus "oral administration" includes buccal and sublingual as well as esophageal administration. Absorption of the agent can occur in any part or parts of the gastrointestinal tract including the mouth, esophagus, stomach, duodenum, jejunum, ileum and colon. The term "dose unit" herein means a portion of a pharmaceutical composition that contains an amount of a therapeutic agent suitable for a single oral administration to provide a therapeutic effect. Typically one dose unit, or a small plurality (up to about 4) of dose units, provides a sufficient amount of the agent to result in the desired effect.

Aminosulfonyl-comprising drug

Each dose unit or small plurality of dose units comprises, in a therapeutically and/or prophylactically effective total amount, a drug of low water solubility that comprises an aminosulfonyl functional group and/or is capable of reacting with a polyethylene glycol or a polyethylene glycol degradation product to form an addition compound. A "drug of low water solubility" or "poorly water solubility drug" herein refers to any drug compound having a solubility in water, measured at 37°C, not greater than about 10 mg/ml, and preferably not greater than about 1 mg/ml. It is contemplated that compositions of the invention are especially advantageous for drugs having a solubility in water, measured at 37°C, not greater than about 0.1 mg/ml.

It will be understood that a therapeutically and/or prophylactically effective amount of a drug for a subject is dependent *inter alia* on the body weight of the subject. A "subject" herein to which a therapeutic agent or composition thereof can be administered includes a human patient of either sex and of any age, and also includes any nonhuman animal, particularly a domestic or companion animal, illustratively a cat, dog or horse.

The term "aminosulfonyl functional group" herein refers to a functional group having the following structure:



wherein the wavy line represents a bond by which the functional group is attached to the rest of the drug molecule; and R is hydrogen or a substituent that preserves ability of polyethylene glycol or a polyethylene glycol degradation product to react with the

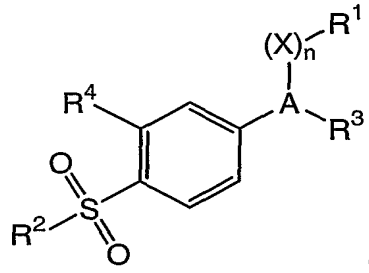
amino group adjacent to R to form an addition compound. Illustrative examples of such substituents include partially unsaturated heterocyclyl, heteroaryl, cycloalkenyl, aryl, alkylcarbonyl, formyl, halo, alkyl, haloalkyl, oxo, cyano, nitro, carboxyl, phenyl, alkoxy, aminocarbonyl, alkoxycarbonyl, carboxyalkyl, cyanoalkyl, hydroxyalkyl, hydroxyl, alkoxyalkyloxyalkyl, haloalkylsulfonyloxy, carboxyalkoxyalkyl, cycloalkylalkyl, alkynyl, heterocyclyloxy, alkylthio, cycloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, heteroarylcarbonyl, alkylthioalkyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-Narylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsufinyl, alkylsulfonyl, *etc.*

Non-limiting illustrative examples of aminosulfonyl-comprising drugs include ABT-751 of Eisai (N-(2-((4-hydroxyphenyl)amino)-3-pyridyl)4-methoxybenzene-sulfonamide); alpiropride; amosulalol; amprenavir; amsacrine; argatroban; asulacrine; azosemide; BAY-38-4766 of Bayer (N-[4-[[[5-(dimethylamino)-1-naphthalenyl] sulfonyl]amino]phenyl]-3-hydroxy-2,2-dimethylpropanamide); bendroflumethiazide; BMS-193884 of Bristol Myers Squibb (N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-[1,1'-biphenyl]-2-sulfonamide); bosentan; bumetanide; celecoxib; chlorthalidone; delavirdine; deracoxib; dofetilide; domitroban; dorzolamide; dronedarone; E-7070 of Eisai (N-(3-chloro-1H-indol-7-yl)-1,4-benzene-disulfonamide); EF-7412 of Schwartz Pharma (N-3-[4-[4-(tetrahydro-1,3-dioxo-1H-pyrrolo[1,2-c]imidazol-2(3H)-yl)butyl]-1-piperazinyl]phenyl]ethanesulfonamide); fenquizone; furosemide; glibenclamide; gliclazide; glimepiride; glipentide; glipizide; gliquidone; glisolamide; GW-8510 of Glaxo SmithKline (4-[[(6,7-dihydro-7-oxo-8H-pyrrolo[2,3-g]benzothiazol-8-ylidene)methyl]amino]-N-2-pyridinylbenzenesulfonamide); GYKI-16638 of Ivax (N-[4-[2-[[2-(2,6-dimethoxyphenoxy)-1-methylethyl]methylamino]ethyl]phenyl] methanesulfonamide);HMR-1098 of Aventis (5-chloro-2-methoxy-N-[2-[4-methoxy-3-[[[(methylamino)thioxomethyl]amino]sulfonyl]phenyl]ethyl]benzamide); hydrochlorothiazide; ibutilide; indapamide; IS-741 of Ishihara (N-[2-[(ethylsulfonyl)

amino]-5-(trifluoromethyl)-3-pyridinyl]cyclohexanecarboxamide); JTE-522 of Japan Tobacco (4-(4-cyclohexyl-2-methyl-5-oxazolyl)-2-fluorobenzenesulfonamide); KCB-328 of Chugai (N-[3-amino-4-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino] ethoxy]phenyl]methanesulfonamide); KT2-962 of Kotobuki (3-[4-[[(4-chlorophenyl) sulfonyl]amino]butyl]-6-(1-methylethyl)-1-azulene sulfonic acid); levosulpiride; LY-295501 (N-[[(3,4-dichlorophenyl)amino]carbonyl]-2,3-dihydro-5-benzofuransulfonamide) and LY-404187 (N-2-(4-(4-cyanophenyl)phenyl)propyl-2-propanesulfonamide) of Eli Lilly; metolazone; naratriptan; nimesulide; NS-49 of Nippon ((R)-N-[3-(2-amino-1-hydroxyethyl)-4-fluorophenyl]methanesulfonamide); ONO-8711 of Ono ((5Z)-6-[(2R,3S)-3-[[[(4-chloro-2-methylphenyl)sulfonyl]amino] methyl]bicyclo[2.2.2]oct-2-yl]-5-hexenoic acid); piretanide; PNU-103657 of Pharmacia (1-[5-methanesulfonamidoindol-2-ylcarbonyl]-4-(N-methyl-N-(3-(2-methylpropyl)-2-pyridinyl)amino)piperidine); polythiazide; ramatroban; RO-61-1790 of Hoffmann LaRoche (N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-[2-(1H-tetrazol-5-yl)-4-pyridinyl]-4-pyrimidinyl]-5-methyl-2-pyridinesulfonamide); RPR-130737 (4-hydroxy-3-[2-oxo-3(S)-[5-(3-pyridyl)thiophen-2-ylsulfonamido] pyrrolidin-1-ylmethyl]benzamide) and RPR-208707 of Aventis; S-18886 (3-[(6-(4-chlorophenylsulfonylamino)-2-methyl-5,6,7,8-tetrahydronaphth]-1-yl)propionic acid) and S-32080 (3-[6-(4-chlorophenylsulfonylamido)-2-propyl-3-(3-pyridyl-methyl)-5,6,7,8-tetrahydronaphthalen-1-yl]propionic acid) of Servier; S-36496 of Kaken (2-sulfonyl-[N-(4-chlorophenyl)sulfonylamino-butyl-N-[(4-cyclobutylthiazol-2-yl)ethenylphenyl-3-yl-methyl]]aminobenzoic acid); sampatrilat; SB-203208 of Glaxo SmithKline (L-phenylalanine, b-methyl-, (4aR,6S,7R,7aS)-4-(aminocarbonyl)-7-[[[[[(2S,3S)-2-amino-3-methyl-1-oxopentyl]amino]sulfonyl] acetyl]amino]-7-carboxy-2,4a,5,6,7,7a-hexahydro-2-methyl-1H-cyclopenta[c]pyridin-6-yl ester, (bS)-); SE-170 of DuPont (2-(5-amidino-1H-indol-3-yl)N-[2′-(aminosulfonyl)-3-bromo(1,1′-biphenyl)-4-yl]acetamide); sivelestat; SJA-6017 of Senju (N-(4-fluorophenylsulfonyl)-L-valyl-L-leucinal); SM-19712 of Sumitomo (4-chloro-N-[[(4-cyano-3-methyl-1-phenyl-1H-pyrazol-5-yl)amino]carbonyl]benzene-sulfonamide); sonepiprazole; sotalol; sulfadiazine; sulfaguanole; sulfasalazine; sulpiride; sulprostone; sumatriptan; T-614 of Toyama (N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]-methanesulfonamide); T-138067 (2,3,4,5,6-

pentafluoro-N-(3-fluoro-4-methoxyphenyl)benzenesulfonamide) and T-900607 (2,3,4,5,6-pentafluoro-N-(3-ureido-4-methoxyphenyl)benzenesulfonamide) of Tularik; TAK-661 of Takeda (2,2-dimethyl-3-[[7-(1-methylethyl)[1,2,4]triazolo[1,5-b]pyridazin-6-yl]oxy]-1-propanesulfonamide); tamsulosin; tezosentan; tipranavir; tirofiban; torasemide; trichloromethiazide; tripamide; valdecoxib; veralipride; xipamide; Z-335 of Zeria (2-[2-(4-chlorophenylsulfonylaminomethyl)indan-5-yl]acetic acid); zafirlukast; zonisamide; and salts thereof.

In a preferred embodiment, the aminosulfonyl-comprising drug is a selective COX-2 inhibitory drug of low water solubility. Suitable selective COX-2 inhibitory drugs are compounds having the formula (IV):



(IV)

wherein:

A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings, preferably a heterocyclyl group selected from pyrazolyl, furanonyl, isoxazolyl, pyridinyl, cyclopentenonyl and pyridazinonyl groups;

X is O, S or CH_2;

n is 0 or 1;

R^1 is at least one substituent selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl, and is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

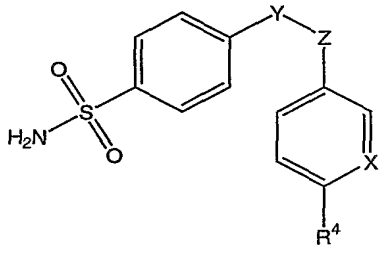
R^2 is an NH_2 group;

R^3 is one or more radicals selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio,

alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl and N-alkyl-N-arylaminosulfonyl, R^3 being optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio; and

R^4 is selected from hydrido and halo.

Particularly suitable selective COX-2 inhibitory drugs are compounds having the formula (V):



(V)

where R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups. Preferred such five- to six-membered rings are cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

Illustratively, compositions of the invention are suitable for celecoxib,

deracoxib, valdecoxib and JTE-522, more particularly celecoxib and valdecoxib.

The invention is illustrated herein with particular reference to celecoxib, and it will be understood that any drug of low water solubility that comprises an aminosulfonyl functional group and/or is capable of reacting with a polyethylene glycol or a polyethylene glycol degradation product to form an addition compound can, if desired, be substituted in whole or in part for celecoxib in compositions herein described.

Where the drug is celecoxib, the composition typically comprises celecoxib in a therapeutically and/or prophylactically effective total amount of about 10 mg to about 1000 mg, preferably about 10 mg to about 400 mg, and more preferably about 100 mg to about 200 mg, per dose unit. Where the drug is a selective COX-2 inhibitory drug other than celecoxib, the amount of the drug per dose unit is therapeutically equivalent to about 10 mg to about 1000 mg of celecoxib.

Where the subject is a child or a small animal (*e.g.*, a dog), for example, an amount of celecoxib relatively low in the typical range of about 10 mg to about 1000 mg is likely to be consistent with therapeutic effectiveness. Where the subject is an adult human or a large animal (*e.g.*, a horse), therapeutic effectiveness is likely to require dose units containing a relatively greater amount of celecoxib. For an adult human, a therapeutically effective amount of celecoxib per dose unit in a composition of the present invention is typically about 50 mg to about 400 mg. Especially preferred amounts of celecoxib per dose unit are about 100 mg to about 200 mg, for example about 100 mg or about 200 mg.

For other selective COX-2 inhibitory drugs, an amount of the drug per dose unit can be in a range known to be therapeutically effective for such drugs. Preferably, the amount per dose unit is in a range providing therapeutic equivalence to celecoxib in the dose ranges indicated immediately above.

Form of compositions of the invention

Compositions of the present invention are preferably in the form of a concentrated solution that may or may not be encapsulated as a discrete article. If encapsulated, preferably a single such article or a small plurality (up to about 10, more preferably no more than about 4) of such articles is sufficient to provide the daily dose. Alternatively, compositions of the present invention are in the form of a

concentrated imbibable liquid. The phrase "imbibable liquid" is used herein to refer to an unencapsulated substantially homogeneous flowable mass, such as a solution or solution/suspension, administered orally and swallowed in liquid form and from which single dose units are measurably removable. The term "substantially homogeneous" with reference to a pharmaceutical composition that comprises several components means that the components are sufficiently mixed such that individual components are not present as discrete layers and do not form concentration gradients within the composition.

A particular dose unit can be selected to accommodate the desired frequency of administration used to achieve a specified daily dose. For example, a daily dosage amount of 400 mg can be accommodated by administration of one 200 mg dose unit, or two 100 mg dose units, twice a day. The amount of the composition that is administered and the dosage regimen for treating the condition or disorder will depend on a variety of factors, including the age, weight, sex and medical condition of the subject, the nature and severity of the condition or disorder, the route and frequency of administration, and the particular drug selected, and thus may vary widely. It is contemplated, however, that for most purposes a once-a-day or twice-a-day administration regimen provides the desired therapeutic efficacy.

A composition of the invention comprises an aminosulfonyl-comprising drug of low water solubility, at least a portion of which is in dissolved or solubilized form in a solvent liquid suitable for oral administration.

The solvent liquid comprises at least one pharmaceutically acceptable polyethylene glycol as a solvent, at least one pharmaceutically acceptable free radical-scavenging antioxidant and optionally one or more additional components, including pharmaceutically acceptable excipients. The term "excipient" herein means any substance, not itself a therapeutic agent, used as a carrier or vehicle for delivery of a therapeutic agent to a subject or added to a pharmaceutical composition to improve its handling, storage, disintegration, dispersion, dissolution, release or organoleptic properties or to permit or facilitate formation of a dose unit of the composition into a discrete article such as a capsule suitable for oral administration. Excipients can include, by way of illustration and not limitation, diluents, disintegrants, dispersants, binding agents, adhesives, wetting agents, lubricants, glidants, crystallization

inhibitors, stabilizers, substances added to mask or counteract a disagreeable taste or odor, flavors, dyes, fragrances, preservatives, and substances added to improve appearance of the composition.

Such optional additional components should be physically and chemically compatible with the other ingredients of the composition and should not be deleterious to the recipient. Importantly, some of the above-listed classes of excipients overlap each other. Compositions of the present invention can be adapted for administration by any suitable oral route by selection of appropriate solvent liquid components and a dosage of the drug effective for the treatment intended. Accordingly, components employed in the solvent liquid can themselves be solids, semi-solids, liquids, or combinations thereof.

An imbibable composition of the invention can be in the form of, for example, a solution, a solution/suspension, an elixir, a syrup, or any other liquid form reasonably adapted for oral administration. Such compositions can also comprise excipients selected from, for example, emulsifying and suspending agents, sweetening and flavoring agents, surfactants and co-surfactants.

Alternatively, as described in detail below, a composition of the present invention can be prepared in the form of discrete unit dose articles, for example, capsules having a wall that illustratively comprises gelatin and/or a turbidity-decreasing polymer such as HPMC, each capsule containing a liquid composition comprising a predetermined amount of drug in a solvent liquid. The liquid composition within the capsule is released by breakdown of the wall on contact with gastrointestinal fluid. The particular mechanism of capsule wall breakdown is not important and can include such mechanisms as erosion, degradation, dissolution, *etc.*

Compositions of the invention can be prepared by any suitable method of pharmacy that includes the step of bringing into association the drug and the components of the solvent liquid. The polyethylene glycol solvent, the free radical-scavenging antioxidant and the other, optional, components of the solvent liquid can be mixed first, prior to addition of the drug; alternatively, the drug can be mixed with the solvent before addition of other components. Order of addition is generally not critical, but it is typically preferred to add the drug to the solvent liquid after adding the antioxidant. In general, celecoxib compositions of the invention are prepared by

uniformly and intimately admixing celecoxib with a solvent liquid in such a way that at least a portion, preferably substantially all, of the celecoxib is dissolved or solubilized in the solvent liquid; and then, if desired, encapsulating the resulting solution or solution/suspension, for example in hard or soft capsules.

A preferred embodiment of the invention is a composition comprising a therapeutically effective amount of an aminosulfonyl-comprising drug of low water solubility, for example celecoxib or valdecoxib, substantially completely dissolved in a solvent liquid comprising at least one pharmaceutically acceptable polyethylene glycol and at least one pharmaceutically acceptable free radical-scavenging antioxidant. In this embodiment, substantially no part of the drug is present in solid particulate form. Compositions of this embodiment can be formulated either in an imbibable or discrete dosage form (*e.g.*, encapsulated). Preferably, concentrated solutions of this embodiment have a drug concentration of about 10% to about 75%, more preferably about 20% to about 75%, by weight of the composition.

Solvent

Any pharmaceutically acceptable polyethylene glycol (PEG) can be used as a solvent in a composition of the invention. Preferably, the PEG has an average molecular weight of about 100 to about 10,000, and more preferably about 100 to about 1,000. Still more preferably, the PEG is of liquid grade. Non-limiting examples of PEGs that can be used in solvent liquids of this invention include PEG-200, PEG-350, PEG-400, PEG-540 and PEG-600. See for example Flick (1998): Industrial Solvents Handbook, 5th ed., Noyes Data Corporation, Westwood, NJ, p. 392. A presently preferred PEG has an average molecular weight of about 375 to about 450, as exemplified by PEG-400.

As pointed out hereinabove, PEGs such as PEG-400 have many desirable properties as solvents for poorly water-soluble drugs. In the case of celecoxib, for example, the drug can be dissolved or solubilized at a very high concentration in PEG-400, enabling formulation of a therapeutically effective dose in a very small volume of solvent liquid. This is especially important where the resulting solution is to be encapsulated, as capsules of a size convenient for swallowing can be prepared containing a therapeutically effective dose even of a drug such as celecoxib having a relatively high dose requirement for efficacy.

However, the present inventors encountered an unexpected problem when celecoxib was formulated in dissolved or solubilized form in PEG-400. During storage of a solution formulation of celecoxib in PEG-400, one or more impurities were generated. These impurities were traced to reaction of the celecoxib not with PEG-400 itself but with a breakdown product of PEG-400. Without being bound by theory, it is believed that the breakdown product that reacts with celecoxib is ethylene oxide. Products of the reaction include addition compounds having chemical structures that have now been determined and are disclosed hereinbelow. It is contemplated that any drug compound having an aminosulfonyl functional group has a potential to react with a polyethylene glycol breakdown product in a similar way.

The problem of chemical instability of such a drug in a polyethylene glycol solvent, or indeed of any drug that can react with polyethylene glycol or a breakdown product thereof to form an addition compound, has now been solved. According to the present invention, presence of a free radical-scavenging antioxidant in the solvent liquid greatly enhances chemical stability of the drug.

Free radical-scavenging antioxidant

Certain drugs present in aqueous preparations are known to be susceptible to oxidative degradation, particularly in the presence of oxygen. Hydrogen peroxide, for example, is a known free radical generator that can produce free radicals that interact with drugs in such preparations so as to cause drug degradation. Antioxidants have been used in the art to limit such peroxide-mediated drug degradation. Generally, in such a situation, antioxidants act by providing electrons and easily available hydrogen atoms that are accepted more readily by the free radicals than are those of the drug being protected. See Ansel *et al.* (1995): Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th Edition, page 117.

The problem faced by the present inventors differs from the above situation in at least two ways. First, according to the present problem it is believed that it is polyethylene glycol, not the drug, that is directly degraded by free radicals. Second, there is strong evidence to suggest that the degradation mechanism is not dependent upon peroxide (*i.e.*, the polyethylene glycol degradation proceeds by an oxygen-independent mechanism).

Surprisingly, we have now discovered that the presence of a small amount of a

free-radical scavenging antioxidant in a composition of the invention greatly improves chemical stability of the drug. This finding is quite different from above-described situations where antioxidants have previously been used to prevent drug degradation. Without being bound by theory, it is believed that a free radical-scavenging antioxidant inhibits, slows or delays polyethylene glycol degradation, thereby limiting or inhibiting chemical interaction between polyethylene glycol degradation products and the drug.

Therefore, a composition of the present invention comprises at least one pharmaceutically acceptable free radical-scavenging antioxidant. A free radical-scavenging antioxidant is to be contrasted with a "non-free radical-scavenging antioxidant", *i.e.*, an antioxidant that does not possess free radical-scavenging properties. Non-limiting illustrative examples of suitable free radical-scavenging antioxidants include α-tocopherol (vitamin E), ascorbic acid (vitamin C) and salts thereof including sodium ascorbate and ascorbic acid palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), fumaric acid and salts thereof, hypophosphorous acid, malic acid, alkyl gallates, for example propyl gallate, octyl gallate and lauryl gallate, sodium thiosulfate, sodium sulfite, sodium bisulfite and sodium metabisulfite. Preferred free radical-scavenging antioxidants are alkyl gallates, vitamin E, BHA and BHT. More preferably the at least one free radical-scavenging antioxidant is propyl gallate.

One or more free radical-scavenging antioxidants are present in compositions of the invention in a total amount effective to substantially reduce formation of an addition compound, typically in a total amount of about 0.01% to about 5%, preferably about 0.01% to about 2.5%, and more preferably about 0.01% to about 1%, by weight of the composition.

Other excipients

Compositions of the invention optionally contain pharmaceutically acceptable excipients other than polyethylene glycol and free radical-scavenging antioxidants. In the case of a solution composition, for example, such excipients can include co-solvents, sweeteners, crystallization inhibitors, preservatives, dispersants, emulsifying agents, *etc.* Through selection and combination of excipients, compositions can be provided exhibiting improved performance with respect to drug concentration,

dissolution, dispersion, emulsification, efficacy, flavor, patient compliance and other properties.

A composition, particularly a solution composition, of the invention optionally comprises one or more pharmaceutically acceptable co-solvents. Non-limiting examples of suitable co-solvents include additional glycols, alcohols, for example ethanol and n-butanol; oleic and linoleic acid triglycerides, for example soybean oil; caprylic/capric triglycerides, for example Miglyol™ 812 of Huls; caprylic/capric mono- and diglycerides, for example Capmul™ MCM of Abitec; polyoxyethylene caprylic/capric glycerides such as polyoxyethylene (8) caprylic/capric mono- and diglycerides, for example Labrasol™ of Gattefossé; propylene glycol fatty acid esters, for example propylene glycol laurate; polyoxyethylene (35) castor oil, for example Cremophor™ EL of BASF; polyoxyethylene glyceryl trioleate, for example Tagat™ TO of Goldschmidt; lower alkyl esters of fatty acids, for example ethyl butyrate, ethyl caprylate and ethyl oleate; and water.

A composition, particularly a solution composition, of the invention optionally comprises a pharmaceutically acceptable fatty acid and a pharmaceutically acceptable organic amine (also referred to herein as a "fatty acid/organic amine pair") in total and relative amounts such that the composition is finely self-emulsifiable in simulated gastric fluid. "Simulated gastric fluid" and its abbreviation "SGF", as the term is used herein, describes an aqueous solution of 0.01M hydrochloric acid and 0.15M sodium chloride, having a pH of about 2. Without being bound by theory, it is believed that a fatty acid/organic amine pair, when present in a composition of the invention, promotes formation of charged fine-emulsion droplets upon exposure of the composition to an aqueous medium such as SGF.

Whether a composition is "finely self-emulsifiable" in SGF as defined herein can illustratively be determined according to Test I.

Test I:

A. A 400 µl aliquot of a test composition is placed into a screw-top, side-arm vessel containing 20 ml SGF (maintained at 37°C throughout the test) to form a test liquid.

B. The test liquid is mildly agitated at 75 rpm for 2 minutes using an orbital shaker, to permit emulsification.

C. A 5–50 μl aliquot of the test liquid is withdrawn through the side-arm using a pipette and is discharged from the pipette into a sampling vessel.

D. A pump (*e.g.*, model RH0CKC-LF, Fluid Metering Inc., Syosset, NY) is used to pull the test liquid from the sampling vessel through a combination scattering/obscuration sensor (*e.g.*, LE400-0.5, Particle Sizing Systems, Santa Barbara, CA) at a rate of 1 ml/minute for a period of 1 minute.

E. Emulsion particles are counted individually by light scattering in the size (*i.e.*, diameter) range from 0.5 to 1 μm and by light obscuration in the size range above 1 μm, using the vendor's software (*e.g.*, Version 1.59).

F. A plot is prepared of number (*i.e.*, unweighted) or volume (*i.e.*, weighted) of emulsion particles versus particle diameter.

G. Integration of the plot, accounting for all dilutions, is performed to estimate total number or volume of emulsion particles present in the test liquid large enough to be detected by the sensor.

H. If Test I results in about 25% or more, by volume, of emulsion particles having a diameter of 1 μm or less, the test composition is deemed to be finely self-emulsifiable.

Preferred fatty acids have a saturated or unsaturated C_{6-24} carbon chain. Non-limiting examples of suitable fatty acids include oleic acid, octanoic acid, caproic acid, caprylic acid, capric acid, eleostearic acid, lauric acid, myristic acid, palmitic acid, stearic acid, icosanoic acid, elaidic acid, linoleic acid, linolenic acid, eicosapentaenoic acid and docosahexaenoic acid. Oleic acid is an especially preferred fatty acid.

Preferred organic amines have a C_{2-8} carbon chain with one or two amine groups. More preferably, organic amines can be selected from C_{2-8} alkyl amines, alkylene diamines, alkanol amines, alkylalkanol amines, glycol ether amines and aryl amines. Non-limiting examples of suitable organic amines include monoethanolamine, diethanolamine, triethanolamine, dimethylaminoethanol, tromethamine, *etc*. Particularly preferred organic amines are tertiary amines, for example triethanolamine and dimethylaminoethanol.

Preferably, if present, a fatty acid/organic amine pair is selected (as to both

type and amount of each component) such that when a composition of the invention is subjected to Test I, at least about 50%and more preferably at least about 75%, by volume, of the emulsion particles counted have a diameter of about 1 μm or less. It is especially preferred that a substantial portion by volume of the emulsion particles counted, more preferably at least about 75%, still more preferably at least about 85%, and most preferably at least about 90%, have a diameter of about 0.5 μm or less.

A preferred mole ratio of fatty acid to amine group(s) in the organic amine is about 5:1 to about 1:100, more preferably about 3:1 to about 1:50, and still more preferably about 2:1 to about 1:10, for example about 1:1. Preferably, if present, the fatty acid and organic amine are collectively present in an amount of about 1% to about 50%, more preferably about 2% to about 30%, and still more preferably about 5% to about 15%, by weight of the composition.

It is believed, without being bound by theory, that a finely self-emulsifiable solution composition of the invention, particularly one having a fatty acid/organic amine pair as described above, will provide the drug in a form that is especially rapidly absorbable in the gastrointestinal tract.

In a solution composition of the invention, the drug, even when finely emulsified, can, upon exposure to the aqueous environment of the gastrointestinal tract, precipitate and agglomerate in a solid, typically crystalline, particulate form. Such precipitation and/or crystallization can adversely impact any rapid-onset benefits obtained by administering a drug in dissolved form, because a drug that has reverted to a crystalline form must undergo the process of dissolution prior to absorption.

Therefore, preferred compositions further comprise a crystallization inhibitor, also referred to herein as a turbidity-decreasing polymer. We have discovered that certain polymers can substantially inhibit precipitation and/or crystallization of a poorly water-soluble drug, when a solution of the drug in a substantially non-aqueous solvent is exposed to SGF. Accordingly, compositions of the present invention preferably comprise a turbidity-decreasing polymer. The polymer can be a cellulosic or non-cellulosic polymer and is preferably substantially water-soluble.

It will be understood that certain polymers are more effective at inhibiting precipitation and/or crystallization of a selected poorly water soluble drug than others, and that not all polymers inhibit precipitation and/or crystallization as described

herein of every poorly water-soluble drug. Whether a particular polymer is useful as a crystallization inhibitor for a particular poorly water soluble drug according to the present invention can be readily determined by one of ordinary skill in the art, for example according to Test II.

Test II:

A. A suitable amount of the drug is dissolved in a solvent (*e.g.*, ethanol, dimethyl sulfoxide or, where the drug is an acid or base, water) to obtain a concentrated drug solution.

B. A volume of water or buffered solution with a fixed pH is placed in a first vessel and maintained at room temperature.

C. An aliquot of the concentrated drug solution is added to the contents of the first vessel to obtain a first sample solution having a desired target drug concentration. The drug concentration selected should be one which produces substantial precipitation and consequently higher apparent absorbance (*i.e.*, turbidity) than a saturated solution having no such precipitation.

D. A test polymer is selected and, in a second vessel, the polymer is dissolved in water or a buffered solution with a fixed pH (identical in composition, pH and volume to that used in step C) in an amount sufficient to form a 0.25% - 2% w/w polymer solution.

E. To form a second sample solution, an aliquot of the concentrated drug solution prepared in step A is added to the polymer solution in the second vessel to form a sample solution having a final drug concentration equal to that of the first sample solution.

F. At 60 minutes after preparation of both sample solutions, apparent absorbance (*i.e.*, turbidity) of each sample solution is measured using light having a wavelength of 650 nm;

G. If the turbidity of the second sample solution is less than the turbidity of the first sample solution, the test polymer is deemed to be a "turbidity-decreasing polymer" and is useful as a crystallization inhibitor for the test drug.

A technician performing Test II will readily find a suitable polymer

concentration for the test within the polymer concentration range provided above, by routine experimentation. In a particularly preferred embodiment, a concentration of the polymer is selected such that when Test II is performed, the apparent absorbance of the second sample solution is not greater than about 50% of the apparent absorbance of the first sample solution.

In another embodiment, compositions of the invention comprise a crystallization inhibitor comprising at least one cellulosic polymer. Preferred cellulosic polymers are selected from HPMC, methylcellulose, ethylcellulose, sodium carboxymethylcellulose and hydroxypropylcellulose. More preferably, the at least one cellulosic polymer is selected from cellulosic polymers having at least a portion of substitutable hydroxyl groups substituted with methoxyl and/or hydroxypropoxyl groups. Still more preferably, the at least one cellulosic polymer is HPMC.

HPMC useful as a crystallization inhibitor according to the invention preferably has a viscosity, 2% in water, of about 100 to about 20,000 cP. HPMCs vary in the degree of substitution of available hydroxyl groups on the cellulosic backbone by methoxyl groups and by hydroxypropoxyl groups. With increasing hydroxypropoxyl substitution, the resulting HPMC becomes more hydrophilic in nature. It is preferred to use HPMC having about 15% to about 35%, more preferably about 19% to about 30%, and most preferably about 19% to about 24%, methoxyl substitution, and having about 3% to about 15%, more preferably about 4% to about 12%, and most preferably about 7% to about 12%, hydroxypropoxyl substitution.

Suitable HPMCs that are relatively hydrophilic in nature are illustratively available under the brand names Methocel™ of Dow Chemical Co. and Metolose™ of Shin-Etsu Chemical Co.

An illustrative presently preferred HPMC is one with substitution type 2208, denoting about 19% to about 24% methoxyl substitution and about 7% to about 12% hydroxypropoxyl substitution, and with a nominal viscosity, 2% in water, of about 4000 cP.

Surprisingly, it has been found that the crystallization inhibitor need not be a component of the solvent liquid. Optionally, a crystallization inhibitor such as HPMC can be a component of a capsule wall wherein a solution composition of the invention is encapsulated. In one embodiment, substantially no HPMC or other crystallization

inhibitor is present in the solvent liquid but the capsule wall comprises HPMC. The capsule wall can even consist predominantly of HPMC.

If present, the crystallization inhibitor is preferably present in a total amount sufficient to substantially inhibit drug crystallization and/or precipitation upon dilution of the composition in SGF. An amount sufficient to "substantially inhibit drug crystallization and/or precipitation" herein means an amount sufficient to prevent, slow, inhibit or delay precipitation of drug from solution and/or to prevent, slow, inhibit or delay formation of crystalline drug particles from dissolved drug particles. For practical purposes, whether an amount of crystallization inhibitor in a given test composition is sufficient to substantially inhibit drug crystallization and/or precipitation can be determined according to Test III, which can also be used to determine whether a particular polymer component is useful as a crystallization inhibitor in a particular composition of the invention.

Test III:

A. A volume of a test composition, either in unencapsulated or encapsulated form, having a polymer component is placed in a volume of SGF to form a mixture having a fixed ratio of about 1 g to about 2 g of the composition per 100 ml of SGF.

B. The mixture is maintained at a constant temperature of about 37°C and is stirred using type II paddles (USP 24) at a rate of 75 rpm for a period of 4 hours.

C. At one or more time-points after at least about 15 minutes of stirring but before about 4 hours of stirring, an aliquot of the mixture is drawn and filtered, for example through a non-sterile Acrodisc™ syringe filter with a 0.8 μm Versapor™ membrane.

D. Filtrate is collected in a vessel.

E. Drug concentration in the filtrate is measured using high performance liquid chromatography (HPLC).

F. The test is repeated identically with a comparative composition that is substantially similar to the test composition except that it lacks the polymer component. Where the polymer component in the test composition is present in the solvent liquid, it is replaced in the

comparative composition by polyethylene glycol solvent. Where the polymer component in the test composition is present in a capsule wall, it is replaced in the comparative composition with gelatin.

G. If the drug concentration in the filtrate resulting from the test composition is greater than that in the filtrate resulting from the comparative composition, the polymer component present in the test composition is deemed to substantially inhibit crystallization and/or precipitation of the drug in SGF.

A crystallization inhibitor such as HPMC, when present in the solvent liquid, is generally present in a total amount of about 1% to about 20%, preferably about 1% to about 15%, and most preferably about 1% to about 10%, by weight of the solvent liquid. Typically, the higher the drug concentration in the composition, the more of the cellulosic polymer will be required to provide a crystallization-inhibiting effect. Generally, the crystallization inhibitor, if present, and the drug are present in a ratio of about 1:100 to about 1:1, preferably about 1:50 to about 1:1 and more preferably about 1:25 to about 1:1, by weight.

A composition of the invention optionally comprises one or more pharmaceutically acceptable sweeteners. Non-limiting examples of suitable sweeteners include mannitol, propylene glycol, sodium saccharin, acesulfame K, neotame and aspartame. Alternatively or in addition, a viscous sweetener such as sorbitol solution, syrup (sucrose solution) or high-fructose corn syrup can be used and, in addition to sweetening effects, can also be useful to increase viscosity and to retard sedimentation. Use of sweeteners is especially advantageous in imbibable compositions of the invention, as these can be tasted by the subject prior to swallowing. An encapsulated composition does not typically interact with the organs of taste in the mouth and use of a sweetener is normally unnecessary.

A composition of the invention optionally comprises one or more pharmaceutically acceptable preservatives other than free radical-scavenging antioxidants. Non-limiting examples of suitable preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate, thimerosal, *etc.*

A composition of the invention optionally comprises one or more

pharmaceutically acceptable wetting agents. Surfactants, hydrophilic polymers and certain clays can be useful as wetting agents to aid in dissolution and/or dispersion of a hydrophobic drug such as celecoxib. Non-limiting examples of suitable surfactants include benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, dioctyl sodium sulfosuccinate, nonoxynol 9, nonoxynol 10, octoxynol 9, poloxamers, polyoxyethylene (8) caprylic/capric mono- and diglycerides (*e.g.*, Labrasol™ of Gattefossé), polyoxyethylene (35) castor oil, polyoxyethylene (20) cetostearyl ether, polyoxyethylene (40) hydrogenated castor oil, polyoxyethylene (10) oleyl ether, polyoxyethylene (40) stearate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80 (*e.g.*, Tween™ 80 of ICI), propylene glycol laurate (*e.g.*, Lauroglycol™ of Gattefossé), sodium lauryl sulfate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, tyloxapol, and mixtures thereof.

Additionally, compositions of the invention optionally comprise one or more pharmaceutically acceptable buffering agents, flavoring agents, colorants, stabilizers and/or thickeners. Buffers can be used to control pH of a formulation and can thereby modulate drug solubility. Flavoring agents can enhance patient compliance by making the composition more palatable, particularly in the case of an imbibable composition, and colorants can provide a product with a more aesthetic and/or distinctive appearance. Non-limiting examples of suitable colorants include D&C Red No. 33, FD&C Red No. 3, FD&C Red No. 40, D&C Yellow No. 10, and C Yellow No. 6.

Solution/suspension compositions

In one embodiment, the solvent liquid, depending on the particular components present therein, is suitable to maintain a first portion of drug in solution to provide a therapeutically effective rapid-onset dose while also maintaining a second portion of the drug undissolved but in suspension. The suspended portion typically provides less immediate release of the drug and so can extend the duration of therapeutic effect, although such extended duration is not a requirement of this embodiment of the invention.

Therefore, according to this embodiment a composition is provided comprising a therapeutically effective amount of a poorly water-soluble

aminosulfonyl-comprising drug, in part dissolved and in part dispersed in a solvent liquid that comprises at least one pharmaceutically acceptable polyethylene glycol and at least one pharmaceutically acceptable free radical-scavenging antioxidant. In this embodiment, part of the drug is in solution and part is in suspension.

Preferably, the components of the solvent liquid are selected such that at least about 15% by weight of the drug is in dissolved or solubilized form in the solvent liquid. One way of modifying a solvent liquid to increase the amount of the poorly water soluble aminosulfonyl-comprising drug in suspension as opposed to solution is to add water in an amount necessary to give the required reduction in solubility of the drug in the solvent liquid.

Depending on the relative importance of rapid onset and sustained action for the indication for which the drug is being administered, the relative proportions of dissolved and suspended drug can be varied significantly. For example, for acute pain indications, about 50% of the drug can be in solution and about 50% of the drug can be dispersed in particulate form. Alternatively, for indications demanding longer acting therapeutic effectiveness, illustratively about 20% of the drug can be in solution and about 80% of the drug can be dispersed in particulate form.

The particulate form of the drug can be generated mechanically, for example by milling or grinding, or by precipitation from solution. Particles formed directly from such processes are described herein as "primary particles" and can agglomerate to form secondary aggregate particles. The term "particle size" as used herein refers to size, in the longest dimension, of primary particles, unless the context demands otherwise. Particle size is believed to be an important parameter affecting the clinical effectiveness of celecoxib and other drugs of low water solubility.

Particle size can be expressed as the percentage of total particles that have a diameter smaller than a given reference diameter. For example, a useful parameter is "D_{90} particle size". By definition, in a batch of a drug that has a D_{90} particle size of 60 μm, 90% of the particles, by volume, have a diameter less than 60 μm. For practical purposes a determination of D_{90} based on 90% by weight rather than by volume is generally suitable.

Compositions of this embodiment preferably have a distribution of suspended drug particle sizes such that D_{90} of the particles, in their longest dimension, is about

0.5 μm to about 200 μm, preferably about 0.5 μm to about 75 μm, and more preferably about 0.5 μm to about 25 μm. For example, where the drug is celecoxib, a decrease in particle size in accordance with this embodiment of the invention generally improves drug bioavailability. In addition or alternatively, suspended celecoxib particles in a composition of the invention preferably have a mean particle size less than about 10 μm, more preferably about 0.1 μm to about 10 μm, and most preferably about 0.5 μm to about 5 μm, for example about 1 μm.

Compositions of this embodiment can optionally comprise additional excipients such as crystallization inhibitors, dispersants, co-solvents, sweeteners, preservatives, emulsifying agents, *etc.*, as described above. Further, compositions of this embodiment can be formulated either in imbibable or discrete dosage form.

Additionally, certain excipients such as suspending agents, thickening agents and flocculating agents can be particularly useful where suspended drug particles are desired, for example in solution/suspension compositions. Through selection and combination of excipients, solution/suspension compositions can be provided exhibiting improved performance with respect to drug concentration, physical stability, efficacy, flavor, and overall patient compliance.

Solution/suspension compositions of the invention optionally comprise one or more pharmaceutically acceptable suspending agents. Suspending agents are used to impart increased viscosity and retard sedimentation. Suspending agents are of various classes including cellulose derivatives, clays, natural gums, synthetic gums and miscellaneous agents. Non-limiting examples of suspending agents that can be used in compositions of the present invention include acacia, agar, alginic acid, aluminum monostearate, attapulgite, bentonite, carboxymethylcellulose calcium, carboxymethylcellulose sodium, carrageenan, carbomer, for example carbomer 910, dextrin, ethylmethylcellulose, gelatin, guar gum, HPMC, methylcellulose, ethylcellulose, ethylhydroxyethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, kaolin, magnesium aluminum silicate, microcrystalline cellulose, microcrystalline cellulose with carboxymethylcellulose sodium, powdered cellulose, silica gel, colloidal silicon dioxide, locust bean gum, pectin, sodium alginate, propylene glycol alginate, tamarind gum, tragacanth, xanthan gum, povidone, veegum, glycyrrhizin, pregelatinized starch, sodium starch glycolate and mixtures

thereof.

In certain circumstances, it can be desirable to use flocculating agents in solution/suspension compositions of the invention. Flocculating agents enable particles to link together in loose aggregates or flocs and include surfactants, hydrophilic polymers, clays and electrolytes. Non-limiting examples of suitable flocculating agents include sodium lauryl sulfate, docusate sodium, benzalkonium chloride, cetylpyridinium chloride, polysorbate 80, sorbitan monolaurate, carboxymethylcellulose sodium, xanthan gum, tragacanth, methylcellulose, PEG, magnesium aluminum silicate, attapulgite, bentonite, potassium dihydrogen phosphate, aluminum chloride, sodium chloride and mixtures thereof.

Discrete dosage forms

It has been found that the demands of a rapid-onset formulation are met surprisingly well by a preparation containing a solution or solution/suspension of the present invention encapsulated as a discrete dosage unit article. Therefore, another embodiment of the present invention is a concentrated composition, either a solution or solution/suspension, wherein the composition is formulated as one or more discrete dose units, for example soft or hard capsules.

Any suitable encapsulation material, for example gelatin or HPMC, can be used. As indicated hereinabove, HPMC can be an advantageous material for use in the capsule wall because it can act as a crystallization inhibitor upon exposure of the composition to gastrointestinal fluid. A polymer component such as HPMC is "present in the capsule wall" or is a "capsule wall component" as described herein if the polymer is (a) dispersed or mixed together with any other capsule wall component(s), (b) the only capsule wall component, or (c) present as a coating on the outside or inside of the capsule wall.

In a presently preferred embodiment, a crystallization inhibitor, preferably a polymer having methoxyl and/or hydroxypropoxyl substitution as described hereinabove, and more preferably HPMC, is present in the capsule wall in a total amount of about 5% to substantially 100%, and preferably about 15% to substantially 100%, by weight of the wall.

The crystallization inhibitor is preferably present in the wall in a total amount sufficient to substantially inhibit drug crystallization and/or precipitation upon

dissolution, dilution and/or degradation of the composition in SGF. For practical purposes, whether an amount of crystallization inhibitor present in the wall of a given test composition is sufficient to substantially inhibit drug crystallization and/or precipitation can be determined according to Test IV, which can also be used to determine whether a particular polymer component is useful as a crystallization inhibitor when present in the capsule wall of a particular composition of the invention.

Test IV:

A. A volume of a solution or solution/suspension as described herein above is enclosed in a capsule comprising a test polymer to form a test composition, and is placed in a volume of SGF to form a mixture having a fixed ratio of about 1 g to about 2 g of the composition per 100 ml of SGF.

B. The mixture is maintained at a constant temperature of about 37°C and is stirred using type II paddles (USP 24) at a rate of 75 rpm for a period of 4 hours.

C. At one or more time-points after at least about 15 minutes of stirring but before about 4 hours of stirring, an aliquot of the mixture is drawn and filtered, for example through a non-sterile Acrodisc™ syringe filter with a 0.8 μm Versapor™ membrane.

D. Filtrate is collected in a vessel.

E. Drug concentration in the filtrate is measured using high performance liquid chromatography (HPLC).

F. The test is repeated identically with a comparative composition comprising a solution or solution/suspension that is substantially similar to the solution or solution/suspension used in Step A but which is enclosed in a capsule comprising no crystallization inhibitor (*i.e.* comprises no polymer or, if a polymer is present, it is a polymer such as gelatin which does not inhibit crystallization and/or precipitation). The polymer component is replaced in the capsule enclosing the comparative composition with gelatin.

G. If the drug concentration in the filtrate resulting from the test composition is greater than that in the filtrate resulting from the

comparative composition, the polymer component present in the capsule wall of the test composition is deemed to be present in an amount sufficient to substantially inhibit crystallization and/or precipitation of the drug in SGF.

In addition to one or more such crystallization inhibitors, a suitable capsule wall can comprise any additional component useful in the art such as gelatin, starch, carrageenan, sodium alginate, plasticizers, potassium chloride, coloring agents, *etc.* A suitable capsule herein may have a hard or soft wall.

Preferably, one to about six, more preferably one to about four, and still more preferably one or two of such discrete dosage units per day provides a therapeutically effective dose of the drug.

Compositions of this embodiment are preferably formulated such that each discrete dosage unit contains about 0.3 ml to about 1.5 ml, more preferably about 0.3 ml to about 1 ml, for example about 0.8 ml or about 0.9 ml, of solution or solution/suspension.

Concentrated solutions or solutions/suspensions can be encapsulated by any method known in the art including the plate process, vacuum process, or the rotary die process. See, for example, Ansel *et al.* (1995) in Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th ed., Williams & Wilkins, Baltimore, MD, pp. 176-182. By the rotary die process, liquid encapsulation material, for example gelatin, flowing from an overhead tank is formed into two continuous ribbons by a rotary die machine and brought together by twin rotating dies. Simultaneously, metered fill material is injected between ribbons at the same moment that the dies form pockets of the ribbons. These pockets of fill-containing encapsulation material are then sealed by pressure and heat, and the capsules are served from the machine.

Soft capsules can be manufactured in different shapes including round, oval, oblong, and tube-shape, among others. Additionally, by using two different ribbon colors, two-tone capsules can be produced.

Capsules that comprise HPMC are known in the art and can be prepared, sealed and/or coated, by way of non-limiting illustration, according to processes disclosed in the patents and publications listed below, each of which is individually incorporated herein by reference.

United States Patent No. 4,250,997 to Bodenmann *et al.*
United States Patent No. 5,264,223 to Yamamoto *et al.*
United States Patent No. 5,756,123 to Yamamoto *et al.*
International Patent Publication No. WO 96/05812.
International Patent Publication No. WO 97/35537.
International Patent Publication No. WO 00/18377.
International Patent Publication No. WO 00/27367.
International Patent Publication No. WO 00/28976.
International Patent Publication No. WO 01/03676.
European Patent Application No. 0 211 079.
European Patent Application No. 0 919 228.
European Patent Application No. 1 029 539.

Non-limiting illustrative examples of suitable HPMC-comprising capsules include XGel™ capsules of Bioprogress and Qualicaps™ of Shionogi.

Imbibable dosage forms

Another embodiment of the present invention is a concentrated composition, either a concentrated solution or a concentrated solution/suspension, that can be directly imbibed or diluted with inert diluents and/or other carriers and imbibed; such compositions of the invention, whether diluted or not, are referred to for convenience herein as "imbibable compositions". Imbibable compositions can be prepared by any suitable method of pharmacy that includes the steps of bringing into association the drug of low water solubility, illustratively celecoxib, and the solvent liquid. Where the drug is celecoxib, compositions of this embodiment preferably contain about 40 mg/ml to about 750 mg/ml, more preferably about 50 mg/ml to about 500 mg/ml, still more preferably about 50 mg/ml to about 350 mg/ml, and most preferably, about 100 mg/ml to about 300 mg/ml, for example about 200 mg/ml, of celecoxib.

In a further embodiment, solutions or solution/suspensions of the invention are provided that are required to be diluted to provide a dilution suitable for direct, imbibable administration. In this embodiment, solutions or solution/suspensions of the present invention are added, in a therapeutically effective dosage amount, to about 1 ml to about 20 ml of an inert liquid. Preferably solutions or solution/suspensions of the present invention are added to about 2 ml to about 15 ml, and more preferably to

about 5 ml to about 10 ml, of inert liquid. The term "inert liquid" as used herein refers to pharmaceutically acceptable, preferably palatable liquid carriers. Such carriers are typically aqueous. Examples include water, fruit juices, carbonated beverages, *etc.*

Utility of compositions that comprise a selective COX-2 inhibitory drug

In a preferred embodiment, compositions of the invention comprise an aminosulfonyl-comprising selective COX-2 inhibitory drug of low water solubility. Compositions of this embodiment are useful in treatment and prevention of a very wide range of disorders mediated by COX-2, including but not restricted to disorders characterized by inflammation, pain and/or fever. Such compositions are especially useful as anti-inflammatory agents, such as in treatment of arthritis, with the additional benefit of having significantly less harmful side effects than compositions of conventional nonsteroidal anti-inflammatory drugs (NSAIDs) that lack selectivity for COX-2 over COX-1. In particular, such compositions have reduced potential for gastrointestinal toxicity and gastrointestinal irritation including upper gastrointestinal ulceration and bleeding, reduced potential for renal side effects such as reduction in renal function leading to fluid retention and exacerbation of hypertension, reduced effect on bleeding times including inhibition of platelet function, and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects, by comparison with compositions of conventional NSAIDs. Thus compositions of the invention comprising a selective COX-2 inhibitory drug are particularly useful as an alternative to conventional NSAIDs where such NSAIDs are contraindicated, for example in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; gastrointestinal bleeding, coagulation disorders including anemia such as hypoprothrombinemia, hemophilia or other bleeding problems; kidney disease; or in patients prior to surgery or patients taking anticoagulants.

Such compositions are useful to treat a variety of arthritic disorders, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis.

Such compositions are also useful in treatment of asthma, bronchitis, menstrual cramps, preterm labor, tendinitis, bursitis, allergic neuritis, cytomegalovirus

infectivity, apoptosis including HIV-induced apoptosis, lumbago, liver disease including hepatitis, skin-related conditions such as psoriasis, eczema, acne, burns, dermatitis and ultraviolet radiation damage including sunburn, and post-operative inflammation including that following ophthalmic surgery such as cataract surgery or refractive surgery.

Such compositions are useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis.

Such compositions are useful in treating inflammation in such diseases as migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury including brain edema, myocardial ischemia, and the like.

Such compositions are useful in treatment of ophthalmic diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue.

Such compositions are useful in treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis, and in bone resorption such as that associated with osteoporosis.

Such compositions are useful for treatment of certain central nervous system disorders, such as cortical dementias including Alzheimer's disease, neurodegeneration, and central nervous system damage resulting from stroke, ischemia and trauma. The term "treatment" in the present context includes partial or total inhibition of dementias, including Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia and senile dementia.

Such compositions are useful in treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome and liver disease.

Such compositions are useful in treatment of pain, including but not limited to postoperative pain, dental pain, muscular pain, and pain resulting from cancer. For example, such compositions are useful for relief of pain, fever and inflammation in a

variety of conditions including rheumatic fever, influenza and other viral infections including common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, and trauma following surgical and dental procedures.

Such compositions are useful for treating and preventing inflammation-related cardiovascular disorders, including vascular diseases, coronary artery disease, aneurysm, vascular rejection, arteriosclerosis, atherosclerosis including cardiac transplant atherosclerosis, myocardial infarction, embolism, stroke, thrombosis including venous thrombosis, angina including unstable angina, coronary plaque inflammation, bacterial-induced inflammation including Chlamydia-induced inflammation, viral induced inflammation, and inflammation associated with surgical procedures such as vascular grafting including coronary artery bypass surgery, revascularization procedures including angioplasty, stent placement, endarterectomy, or other invasive procedures involving arteries, veins and capillaries.

Such compositions are useful in treatment of angiogenesis-related disorders in a subject, for example to inhibit tumor angiogenesis. Such compositions are useful in treatment of neoplasia, including metastasis; ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, macular degeneration, retrolental fibroplasia and neovascular glaucoma; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemangiomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis.

Such compositions are useful in prevention and treatment of benign and malignant tumors and neoplasia including cancer, such as colorectal cancer, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer, skin cancer such as squamous cell and basal cell cancers,

prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. Neoplasias for which compositions of the invention are contemplated to be particularly useful are gastrointestinal cancer, Barrett's esophagus, liver cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer. Such compositions can also be used to treat fibrosis that occurs with radiation therapy. Such compositions can be used to treat subjects having adenomatous polyps, including those with familial adenomatous polyposis (FAP). Additionally, such compositions can be used to prevent polyps from forming in patients at risk of FAP.

Such compositions inhibit prostanoid-induced smooth muscle contraction by inhibiting synthesis of contractile prostanoids and hence can be of use in treatment of dysmenorrhea, premature labor, asthma and eosinophil-related disorders. They also can be of use for decreasing bone loss particularly in postmenopausal women (*i.e.*, treatment of osteoporosis), and for treatment of glaucoma.

Because of the rapid onset of therapeutic effect that can be exhibited by compositions of the invention, these compositions have particular advantages over prior formulations for treatment of acute COX-2 mediated disorders, especially for relief of pain, for example in headache, including sinus headache and migraine.

Preferred uses for compositions of the present invention are for treatment of rheumatoid arthritis and osteoarthritis, for pain management generally (particularly post-oral surgery pain, post-general surgery pain, post-orthopedic surgery pain, and acute flares of osteoarthritis), for prevention and treatment of headache and migraine, for treatment of Alzheimer's disease, and for colon cancer chemoprevention.

For treatment of rheumatoid arthritis or osteoarthritis, such compositions of the invention can be used to provide a daily dosage of celecoxib of about 50 mg to about 1000 mg, preferably about 100 mg to about 600 mg, more preferably about 150 mg to about 500 mg, still more preferably about 175 mg to about 400 mg, for example about 200 mg. A daily dose of celecoxib of about 0.7 to about 13 mg/kg body weight, preferably about 1.3 to about 8 mg/kg body weight, more preferably about 2 to about 6.7 mg/kg body weight, and still more preferably about 2.3 to about 5.3 mg/kg body weight, for example about 2.7 mg/kg body weight, is generally appropriate when administered in a composition of the invention. The daily dose can be administered in

one to about four doses per day, preferably one or two doses per day.

For treatment of Alzheimer's disease or cancer, such compositions of the invention can be used to provide a daily dosage of celecoxib of about 50 mg to about 1000 mg, preferably about 100 mg to about 800 mg, more preferably about 150 mg to about 600 mg, and still more preferably about 175 mg to about 400 mg, for example about 400 mg. A daily dose of about 0.7 to about 13 mg/kg body weight, preferably about 1.3 to about 10.7 mg/kg body weight, more preferably about 2 to about 8 mg/kg body weight, and still more preferably about 2.3 to about 5.3 mg/kg body weight, for example about 5.3 mg/kg body weight, is generally appropriate when administered in a composition of the invention. The daily dose can be administered in one to about four doses per day, preferably one or two doses per day.

For pain management generally and specifically for treatment and prevention of headache and migraine, such compositions of the invention can be used to provide a daily dosage of celecoxib of about 50 mg to about 1000 mg, preferably about 100 mg to about 600 mg, more preferably about 150 mg to about 500 mg, and still more preferably about 175 mg to about 400 mg, for example about 200 mg. A daily dose of celecoxib of about 0.7 to about 13 mg/kg body weight, preferably about 1.3 to about 8 mg/kg body weight, more preferably about 2 to about 6.7 mg/kg body weight, and still more preferably about 2.3 to about 5.3 mg/kg body weight, for example about 2.7 mg/kg body weight, is generally appropriate when administered in a composition of the invention. The daily dose can be administered in one to about four doses per day. Administration at a rate of one 50 mg dose unit four times a day, one 100 mg dose unit or two 50 mg dose units twice a day or one 200 mg dose unit, two 100 mg dose units or four 50 mg dose units once a day is preferred.

For selective COX-2 inhibitory drugs other than celecoxib, appropriate doses can be selected by reference to the patent literature cited hereinabove.

Besides being useful for human treatment, such compositions of the invention are useful for veterinary treatment of companion animals, exotic animals, farm animals, and the like, particularly mammals. More particularly, such compositions of the invention are useful for treatment of COX-2 mediated disorders in horses, dogs and cats.

This embodiment of the invention is further directed to a therapeutic method

of treating a condition or disorder where treatment with a COX-2 inhibitory drug is indicated, the method comprising oral administration of a composition of the invention to a subject in need thereof. The dosage regimen to prevent, give relief from, or ameliorate the condition or disorder preferably corresponds to once-a-day or twice-a-day treatment, but can be modified in accordance with a variety of factors. These include the type, age, weight, sex, diet and medical condition of the subject and the nature and severity of the disorder. Thus, the dosage regimen actually employed can vary widely and can therefore deviate from the preferred dosage regimens set forth above.

Initial treatment can begin with a dose regimen as indicated above. Treatment is generally continued as necessary over a period of several weeks to several months or years until the condition or disorder has been controlled or eliminated. Subjects undergoing treatment with a composition of the invention can be routinely monitored by any of the methods well known in the art to determine effectiveness of therapy. Continuous analysis of data from such monitoring permits modification of the treatment regimen during therapy so that optimally effective doses are administered at any point in time, and so that the duration of treatment can be determined. In this way, the treatment regimen and dosing schedule can be rationally modified over the course of therapy so that the lowest amount of the composition exhibiting satisfactory effectiveness is administered, and so that administration is continued only for so long as is necessary to successfully treat the condition or disorder.

Compositions of the present embodiment can be used in combination therapies with opioids and other analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic (i.e. non-addictive) analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists and sodium channel blockers, among others. Preferred combination therapies comprise use of a composition of the invention with one or more compounds selected from aceclofenac, acemetacin, *e*-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid (aspirin), *S*-adenosylmethionine, alclofenac, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac, aminochlorthenoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline,

aminopropylon, aminopyrine, amixetrine, ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, α-bisabolol, bromfenac, *p*-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphene, carprofen, carsalam, chlorobutanol, chlorthenoxazin, choline salicylate, cinchophen, cinmetacin, ciramadol, clidanac, clometacin, clonitazene, clonixin, clopirac, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cropropamide, crotethamide, desomorphine, dexoxadrol, dextromoramide, dezocine, diampromide, diclofenac sodium, difenamizole, difenpiramide, diflunisal, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfazone, enfenamic acid, epirizole, eptazocine, etersalate, ethenzamide, ethoheptazine, ethoxazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, floctafenine, flufenamic acid, flunoxaprofen, fluoresone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate, indomethacin, indoprofen, isofezolac, isoladol, isomethadone, isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac, *p*-lactophenetide, lefetamine, levorphanol, lofentanil, lonazolac, lornoxicam, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, meclofenamic acid, mefenamic acid, meperidine, meptazinol, mesalamine, metazocine, methadone hydrochloride, methotrimeprazine, metiazinic acid, metofoline, metopon, mofebutazone, mofezolac, morazone, morphine, morphine hydrochloride, morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen, narceine, nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol, normethadone, normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin,

oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, parsalmide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenyramidol, piketoprofen, piminodine, pipebuzone, piperylone, piprofen, pirazolac, piritramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid, ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide *o*-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sufentanil, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, tramadol, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen and zomepirac (see The Merck Index, 12th Edition (1996), Therapeutic Category and Biological Activity Index, lists therein headed "Analgesic", "Anti-inflammatory" and "Antipyretic").

Particularly preferred combination therapies comprise use of a composition of this embodiment with an opioid compound, more particularly where the opioid compound is codeine, meperidine, morphine or a derivative thereof.

The compound to be administered in combination with a selective COX-2 inhibitory drug can be formulated separately from the drug or co-formulated with the drug in a composition of the invention. Where a selective COX-2 inhibitory drug is co-formulated with a second drug, for example an opioid drug, the second drug can be formulated in immediate-release, rapid-onset, sustained-release or dual-release form.

In an embodiment of the invention, particularly where the COX-2 mediated condition is headache or migraine, the present selective COX-2 inhibitory drug composition is administered in combination therapy with a vasomodulator, preferably a xanthine derivative having vasomodulatory effect, more preferably an alkylxanthine compound.

Combination therapies wherein an alkylxanthine compound is co-administered with a selective COX-2 inhibitory drug composition as provided herein are embraced by the present embodiment of the invention whether or not the alkylxanthine is a vasomodulator and whether or not the therapeutic effectiveness of the combination is

to any degree attributable to a vasomodulatory effect. The term "alkylxanthine" herein embraces xanthine derivatives having one or more C_{1-4} alkyl, preferably methyl, substituents, and pharmaceutically acceptable salts of such xanthine derivatives. Dimethylxanthines and trimethylxanthines, including caffeine, theobromine and theophylline, are especially preferred. Most preferably, the alkylxanthine compound is caffeine.

The total and relative dosage amounts of the selective COX-2 inhibitory drug and of the vasomodulator or alkylxanthine are selected to be therapeutically and/or prophylactically effective for relief of pain associated with the headache or migraine. Suitable dosage amounts will depend on the particular selective COX-2 inhibitory drug and the particular vasomodulator or alkylxanthine selected. For example, in a combination therapy with celecoxib and caffeine, typically the celecoxib will be administered in a daily dosage amount of about 50 mg to about 1000 mg, preferably about 100 mg to about 600 mg, and the caffeine in a daily dosage amount of about 1 mg to about 500 mg, preferably about 10 mg to about 400 mg, more preferably about 20 mg to about 300 mg.

The vasomodulator or alkylxanthine component of the combination therapy can be administered in any suitable dosage form by any suitable route, preferably orally. The vasomodulator or alkylxanthine can optionally be coformulated with the selective COX-2 inhibitory drug in a single oral dosage form. Thus a solution or solution/suspension formulation of the invention optionally comprises both an aminosulfonyl-comprising selective COX-2 inhibitory drug and a vasomodulator or alkylxanthine such as caffeine, in total and relative amounts consistent with the dosage amounts set out hereinabove.

The phrase "in total and relative amounts effective to relieve pain", with respect to amounts of a selective COX-2 inhibitory drug and a vasomodulator or alkylxanthine in a composition of the present embodiment, means that these amounts are such that (a) together these components are effective to relieve pain, and (b) each component is or would be capable of contribution to a pain-relieving effect if the other component is or were not present in so great an amount as to obviate such contribution.

EXAMPLES

Example 1

Six celecoxib solution formulations SF-1 to SF-6 were prepared having components as shown in Table 1. In each case the solvent liquid consisted of PEG-400, either alone (SF-1) or together with at least one free radical-scavenging antioxidant (SF-2 to SF-6). Celecoxib was present in solution at a concentration of 50 mg/g in all formulations. Antioxidant amounts are shown as % weight/weight.

Table 1. Composition of celecoxib solution formulations SF-1 to SF-6

Formulation	Components
SF-1	Celecoxib, PEG-400
SF-2	Celecoxib, PEG-400, 0.1% vitamin E
SF-3	Celecoxib, PEG-400, 0.1% BHA
SF-4	Celecoxib, PEG-400, 0.1% BHT
SF-5	Celecoxib, PEG-400, 0.1% propyl gallate
SF-6	Celecoxib, PEG-400, 0.05% BHA, 0.05% BHT

Example 2

A gradient HPLC assay was used to determine impurities in celecoxib solution formulations SF-1 to SF-6 of Example 1 after storage at various temperatures for different periods of time. Solution formulation samples were drawn and were dissolved in methanol to obtain a celecoxib concentration of about 0.4 to about 0.5 mg/ml prior to injection. Chromatographic conditions were as follows: (a) flow rate: 1 ml/min.; (b) detection: UV 254 nm; (c) injection volume: 10 µl; (d) column: 5 µm Supercosil, LC-DP, 250 x 4.6 mm; (e) column temperature: 40°C; (f) mobile phase A: 10 mM NH_4AC or KH_2PO_4, pH 3; (g) mobile phase B: 100% acetonitrile; (h) running time: 45 minutes. Data are shown in Tables 2 and 3.

Table 2. Impurity level (%) in formulations SF-1 to SF-5 following storage

	days stored at 70°C							
Formulation	**9**	**14**	**16**	**20**	**28**	**33**	**35**	**90**
SF-1	2.9		3.7		7.6		12.6	
SF-2		0.02		0.02		0.02		2.8
SF-3		0.02		0.02		0.02		0.09
SF-4		0.03		0.04		0.06		0.30
SF-5		ND		ND		ND		0.15

ND = None detected

Table 3. Impurity level (%) in formulations SF-1, SF-2, SF-5 and SF-6 following storage at different temperatures

Formulation	Days	Temperature			
		50°C	40°C	25°C	4°C
SF-1	0	0.00	0.00	0.00	0.00
	7	0.09			
	21	4.12	0.11	0.00	
	31	6.25			0.00
	74	7.83	5.40	0.08	0.00
	131	7.85	6.87	0.44	0.00
SF-2	0	0.00	0.00	0.00	0.00
	7	0.00			
	21	0.02	0.00	0.00	
	31	0.01			0.00
	74	0.06	0.02	0.00	0.00
	131	0.07	0.01	0.00	0.00
SF-5	0	0.00	0.00	0.00	0.00
	7	0.02			
	21	0.05	0.03	0.02	
	31	0.05			0.00
	74	0.15	0.11	0.03	0.00
	131	0.20	0.09	0.02	0.00
SF-6	0	0.00	0.00	0.00	0.00
	7	0.00			
	21	0.01	0.01	0.00	
	31	0.01			0.00
	74	0.03	0.02	0.01	0.00
	131	0.06	0.01	0.00	0.00

The data in Tables 2 and 3 indicate that the presence of a small amount of a free radical-scavenging antioxidant such as vitamin E, butyl gallate, BHA or BHT greatly improves chemical stability of celecoxib dissolved in PEG-400 by comparison with compositions comprising no such antioxidant.

Example 3

Solution formulation SF-1 of Example 1 was bubbled with ethylene oxide, a putative source of free radicals, for 15 minutes, and was then stored at 70°C for 10 days. After storage, the formulation was analyzed for the presence of impurities. Addition compounds detected therein were isolated by reversed-phase, semi-preparative HPLC. A 20 x 250 mm Kromasil C18 column was employed with either an isocratic or a gradient, acetonitrile-aqueous trifluoroacetic acid mobile phase.

Detection was accomplished at 254 nm. Pooled fractions containing individual addition compounds, herein referred to as Peak 1, Peak 2 and Peak 3 addition compounds, were concentrated, desalted and reduced in chemical noise-causing components by trapping on a 7 x 300 mm Hamilton PRP-1 column. The eluent from the trapping column containing the individual addition compounds was freeze-dried to yield the final isolates. Peak 1 addition compound was 99% pure and Peak 2 addition compound was >99% pure by analytical HPLC. Peak 3 addition compound was 81% pure by analytical HPLC.

Analytical HPLC was also used to collect analytical scale peak cuts for mass spectrometric analysis on a PE Sciex Q-Star Qq-TOF mass spectrometer. Survey and product ion scans, as well as high resolution mass measurements for empirical formula determination were acquired in μESI (micro-electrospray ionization) mode. High resolution mass spectral information on Peak 1 and Peak 2 addition compounds were obtained on a Finnigan MAT-900ST mass spectrometer operating in μESI mode. Accurate mass measurement for Peak 1 addition compound was carried out by linear E-scan peak matching at a resolution of 7,400 (m/Δm 10% valley definition) using the reference ions from PEG-400, $(C_2H_4O)_9H_2ONa$ at 437.23627 and $(C_2H_4O)_{10}H_2ONa$ at 481.26248 daltons, respectively, to match against the sample pseudo-molecular ion. Accurate mass measurement for Peak 2 addition compound was carried out by linear E-scan peak matching at a resolution of 7,100 (m/Δm 10% valley definition) using the reference ions from PEG-400 $(C_2H_4O)_8H_2ONa$ at 393.21005 and $(C_2H_4O)_9H_2ONa$ at 437.23627 daltons, respectively, to match against the sample pseudo-molecular ion.

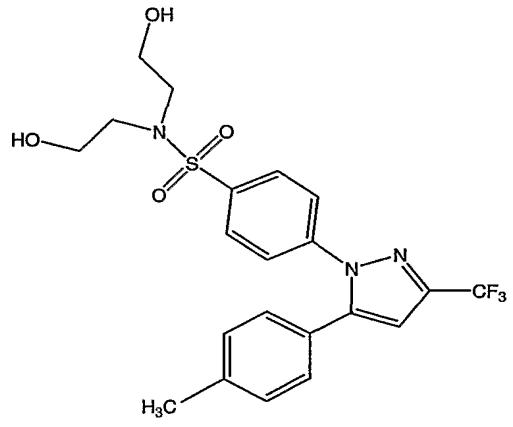
NMR samples were prepared in a nitrogen glove box and dissolved in 150 μl dimethyl sulfoxide-d_6. Data were acquired on a Varian INOVA 400 NMR spectrometer operating at a proton frequency of 399.80 MHz, and equipped with a Nalorac inverse geometry, micro-gradient probe. Experiments were used directly from the vendor's standard library with no modifications.

Peak 1

Celecoxib and Peak 1 addition compound were individually mounted on gold-coated microscope slides for IR and Raman analyses. Micro-IR specular reflectance data were collected from 4000 → 650 cm^{-1} at 4-cm^{-1} resolution on a Nicolet 760 spectrometer equipped with a liquid nitrogen cooled MCT detector. Sensitivity,

expressed as instrument gain, was 8. Data were processed as a Fourier transform utilizing a Happ-Genzel apodization function and plotted as % transmittance *vs.* frequency. The final spectra were the sum of 200 individual scans. Micro-Raman data were collected from 3700 → 100 cm^{-1} on a Nicolet 960 FT-Raman spectrometer, equipped with a liquid nitrogen cooled germanium detector. Sensitivity, expressed as instrument gain, was 64. Data were processed as a Fourier transform utilizing a Happ-Genzel apodization function and plotted as absorbance *vs.* frequency. The final spectra were the sum of 10,000 individual scans.

The molecular weight of Peak 1 addition compound was found to be 469 daltons, 88 daltons heavier than celecoxib and indicative of addition of two ethanolic moieties. The molecular weight was confirmed by high resolution peak matching, of an analytical peak cut, as 469.12831 daltons, within 0.2 ppm of theory for $C_{21}H_{22}F_3N_3O_4S$. The accurate mass of Peak 1 addition compound, less the ionizing proton, was measured as 469.12826 daltons. The empirical formula for best fit using the valence rules was $C_{21}H_{22}F_3N_3O_4S$ and within 0.1 ppm in mass from theory, thus confirming the molecular weight of this product. Peak 1 addition compound is believed to be N,N-bis(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, having the structure (V):



(V)

NMR analysis of Peak 1 addition compound produced similar data to those for the bulk drug. A major difference existed in the absence of the $-SO_2NH_2$ protons, and the inclusion of resonances consistent with the presence of two $-CH_2CH_2OH$ functionalities. The methylene protons and carbons exhibited distinct chemical shifts that are consistent with the proposed structure.

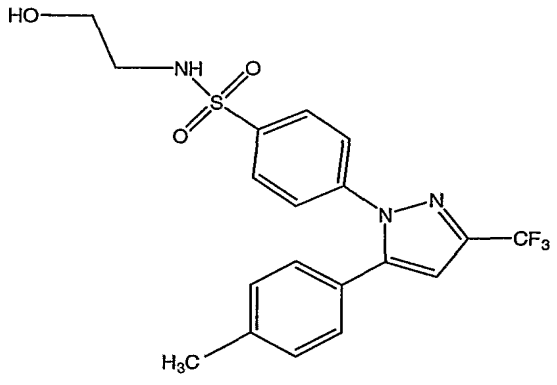
The IR and Raman spectra of celecoxib and Peak 1 addition compound are very similar, indicating that the bulk of the structure is the same as that of celecoxib. Several spectral differences, however, between the two molecules are evident. The two N-H stretching vibrations in the spectrum of celecoxib at 3236 and 3342 cm^{-1} are missing in the data for Peak 1 addition compound, indicating the amino group present in celecoxib is not present in Peak 1 addition compound. The N-H vibrations in the IR spectrum for celecoxib are replaced by an intense, broad absorbance centered at 3430 cm^{-1} in the analogous data for Peak 1 addition compound. This broad band is typical of an O-H stretch, but is much too intense to result from a single hydroxyl group, indicating that Peak 1 addition compound possesses at least two OH groups, in place of the NH_2 group present in celecoxib. Another major spectral difference between the vibrational spectra for celecoxib and Peak 1 addition compound are the presence of Raman C-H stretching vibrational bands for Peak 1 addition compound at 2967 and 2991 cm^{-1} that are not present in the analogous data for celecoxib. These differences indicate the presence of additional CH_2 groups in the addition compound, compared to celecoxib. Both the IR and Raman data are consistent with the proposed structure.

The compound having the structure (V) is believed to be new and is useful as an analytical marker, for example in detecting stability of celecoxib in pharmaceutical compositions where the celecoxib is or has been exposed to polyethylene glycol or ethylene oxide, and/or as a selective cyclooxygenase-2 inhibitory drug or a pro-drug thereof.

Peak 2

The molecular weight of Peak 2 addition compound was found to be 425 daltons, 44 daltons heavier than celecoxib and indicative of the addition of one ethanolic moiety. The molecular weight was confirmed by high resolution peak matching, of an analytical peak cut, as 425.10239 daltons, within 0.9 ppm of theory for $C_{19}H_{18}F_3N_3O_3S$. The accurate mass of Peak 2 addition compound, less the ionizing proton, was measured as 425.10168 daltons. The empirical formula for best fit using the valence rules was $C_{19}H_{18}F_3N_3O_3S$ and within 1.0 ppm in mass from theory, thus confirming the molecular weight of this compound. Peak 2 addition compound is believed to be N-(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-

(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, having the structure (VI):



(VI)

The NMR data for Peak 2 addition compound were similar to those for Peak 1 addition compound in that this isolate also exhibited the $-CH_2CH_2OH$ functionality, but proton integrations identified the presence of only one ethanol substituent. The presence of an -NH- group was also apparent in the proton spectrum. The proton and carbon chemical shifts were in accordance with the proposed structure.

The compound having the structure (VI) is believed to be new and is useful as an analytical marker, for example in detecting stability of celecoxib in pharmaceutical compositions where the celecoxib is or has been exposed to polyethylene glycol or ethylene oxide, and/or as a selective cyclooxygenase-2 inhibitory drug and/or a pro-drug thereof.

Peak 3

Peak 3 addition compound was present in insufficient concentration for an adequate isolate to be obtained for spectroscopic analysis.

Example 4

Three celecoxib (10 mg/g) solutions (with methanol as solvent), one containing no peroxide (S1), one containing 150 ppm hydrogen peroxide (S2), and one containing 150 ppm *t*-butyl-peroxide (S3), were prepared. HPLC analysis, as described in Example 2, was performed to determine the presence or absence of impurities following storage at different temperatures for various periods of time (Table 4).

Table 4. Chemical stability of celecoxib solutions S1–S3

Solution	Time	Total impurity level (%)		
		4°C	25°C	50°C
S1	0	0.15	0.15	0.15
	1 week	0.15	0.15	0.54
	2 weeks		0.14	1.57
	3 weeks, then 3 days at 70°C			2.40
S2	0	0.15	0.15	0.15
	1 week	0.15	0.15	0.46
	2 weeks		0.14	0.94
	3 weeks, then 3 days at 70°C			1.60
S3	0	0.15	0.15	0.15
	1 week	0.15	0.15	0.33
	2 weeks		0.13	0.92
	3 weeks, then 3 days at 70°C			2.00

These data indicate that the presence of hydrogen peroxide or *t*-butyl-peroxide at a concentration of 150 ppm does not affect celecoxib stability in methanol. These data are consistent with the conclusion that chemical instability in a system comprising an aminosulfonyl-comprising drug, for example celecoxib, and a polyethylene glycol, is not peroxide-mediated.

Example 5

Two celecoxib solution formulations, SF-7, and SF-8, and two vehicle (placebo) solution formulations, SF-9 and SF-10, were prepared having components shown in Table 5.

Table 5. Composition (mg) of solution formulations SF-7 to SF-10

Component	SF-7	SF-8	SF-9	SF-10
Celecoxib	200	200		
Water USP	26	26	26	26
HPMC (E5)	38		38	
Ethanol	113	100	113	100
PEG-400	271	322	271	322
Polyvinylpyrrolidone	47	47	47	47
Polysorbate 80	217	217	217	217
Tromethamine	26	26	26	26
Oleic acid	61	61	61	61
Propyl gallate NF	1	1	1	1
Total	1000	1000	800	800

After storage for 90 days at different temperatures, the fraction of the initial

1 mg/g propyl gallate remaining in each formulation was measured via gradient HPLC. Samples of all formulations were dissolved in methanol to obtain a suitable concentration prior to injection. Chromatographic conditions were as follows: (a) flow rate: 1 ml/min.; (b) detection: UV 254 nm; (c) injection volume: 15 μl; (d) column: 3.5 μm Zorbax XBD-C8, 50 x 4.6 mm; (e) column temperature: 25°C; (f) mobile phase A: 0.1% TFA in water; (g) mobile phase B: 0.1% TFA in acetonitrile; (h) running time: 16 minutes. Data are shown in Table 6.

Table 6. Loss of propyl gallate in solution formulations SF-7 to SF-10 after storage for 90 days

	Propyl gallate (% of theoretical) remaining			
Temperature (°C)	**SF-7**	**SF-8**	**SF-9**	**SF-10**
4	87	104	108	126
25	42	74	36	66
40	10	33	10	24
50	0	13	0	19
70	0	0	0	7

These data indicate that, in formulations comprising an aminosulfonyl-comprising drug (celecoxib in the present example) and in those without such a drug, propyl gallate is consumed at a substantially equal rate over 90 days. Moreover, the rate of consumption is temperature dependent with increasing rate as temperature increases. These results suggest that the free radical-scavenging antioxidant is consumed via a non drug-mediated mechanism, and support the present theory that drug stabilization results from an interaction between polyethylene glycol degradation products and the free radical-scavenging antioxidant.

Example 6

A celecoxib solution formulation, SF-11, was prepared having the composition shown in Table 7.

Table 7. Composition (mg/g) of celecoxib solution formulation SF-11

Component	SF-11
Celecoxib	200
Water USP	26
HPMC (E5)	38
Ethanol	113
PEG 400	271
PVP	47
Polysorbate 80	217
Tromethamine	26
Oleic acid	61
Propyl gallate NF	1
Total	1000

One gram of formulation SF-11 was individually placed into each of several hard gelatin capsules (Capsugel) to form Test Composition 1.

A celecoxib suspension for comparative purposes was prepared as follows:

A. Tween™ 80, 5.0 g, was placed in a volumetric flask.

B. Ethanol was added (to 100 ml) to form a mixture and the mixture was swirled to form a uniform solution.

C. A 5 ml aliquot of the uniform solution was transferred to a fresh 100 ml bottle containing 200 mg celecoxib, to form a premix.

D. Apple juice, 75 ml, was added to the premix to form an intermediate celecoxib suspension.

E. The intermediate celecoxib suspension was left to stand for 5 minutes, and was then shaken to form a celecoxib suspension for comparative purposes.

Bioavailability parameters resulting from administration of Test Composition 1, in comparison with the comparative celecoxib suspension composition of Example 5 and with a commercial celecoxib (Celebrex® of Pharmacia) 200 mg capsule, to human subjects were evaluated in a 24-subject, randomized, four period, balanced, crossover study. A fourth composition, not relevant to the present invention, was also included in the study but is not reported here. Study duration was approximately 15 days and subjects were randomly given one of each of the four dosage forms on days 1, 5, 9 and 12; administration of each dose was preceded by an 8 hour fasting period and was accompanied by 180 ml of water. Plasma blood levels for each subject were

measured at pre-dose and at 15, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours after dosage administration. C_{max} and AUC were calculated from the data in accordance with standard procedure in the art. As shown in Table 8, ingestion of Test Composition 1 resulted in a C_{max} more than 2.5 times greater than resulted from ingestion of the comparative celecoxib suspension or the commercial celecoxib capsule. Ingestion of Test Composition 1 also resulted in an AUC 43% greater than, and a T_{max} substantially similar to, that resulting from ingestion of the comparative celecoxib suspension.

Table 8. *In vivo* bioavailability of celecoxib in human subjects

Parameter	Commercial capsule	Comparative suspension	Test composition 1
C_{max} (ng/ml)	621	804	2061
T_{max} (hr)	2.15	0.97	1.03
AUC (ng/ml)*hr	5060	4892	7593

Example 7

Two celecoxib solution formulations, SF-12 and SF-13, and two placebo solution formulations, P-2 and P-3, were prepared having compositions shown in Table 9.

Table 9. Composition (mg) of celecoxib solution formulations SF-12 and SF-13 and placebo solution formulations P-2 and P-3

Component	SF-12	SF-13	P-2	P-3
Celecoxib	100	200	-	-
Water USP	13	26	15.1	30.2
HPMC (E5)	19	38	22.1	44.2
Ethanol	56.5	113	65.7	131.4
PEG 400	135.5	271	157.5	315
PVP	23.5	47	27.3	54.6
Polysorbate 80	108.5	217	126.1	252.3
Tromethamine	13	26	15.1	30.2
Oleic acid	30.5	61	35.5	70.9
Propyl gallate NF	0.5	1	0.6	1.2
Total	500	1000	465	930

Amounts of 500 mg and 1000 mg of solution formulations SF-12 and SF-13 respectively were individually placed into each of several soft gelatin capsules to form Test Compositions 2 (100 mg celecoxib) and 3 (200 mg celecoxib), respectively. Test

Composition 4 consisted of two capsules of Test Composition 3 resulting in a 400 mg celecoxib dose. Placebo solution formulations P-2 and P-3 were filled into soft capsules corresponding in size with those containing solution formulations SF-12 and SF-13, respectively, to form Placebo Composition 2 and Placebo Composition 3.

A randomized, double-blind, active and placebo controlled, single-dose parallel group study was performed in order to assess the analgesic efficacy of Test Compositions 2, 3 and 4 in comparison with appropriate and visually matching placebo, in a human post-oral surgery pain model.

Post-surgical patients (after extraction of two or more impacted third molars requiring bone removal) who reported moderate or severe post-oral surgery pain on a categorical pain scale (CPS; 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain), and a baseline pain intensity ≥50 mm on a visual analog scale (VAS; whereby patient locates a sliding bar representing his or her level of pain on a 100 mm horizontal scale with the left edge (0 mm) marked "no pain" and the right edge (100 mm) marked "worst pain") within 6 hours after completion of surgery were selected and randomized for study.

Each patient was randomized to one of four treatment groups (approximately 55 per group) and, 6 hours after completion of surgery, received the study medication assigned to his or her group from both Bottle A and Bottle B as shown in the medication schedule found in Table 10. Two additional compositions, not illustrative of the present invention, were also included in the study but are not reported here.

Table 10. Schedule of study medication given to patients in treatment groups 1–4

Treatment Group	Bottle A (1 capsule)	Bottle B (2 capsules)
1. (Placebo)	1 x Placebo Composition 2	2 x Placebo Composition 3
2. (Test composition 2)	1 x Test Composition 2	2 x Placebo Composition 3
3. (Test composition 3)	1 x Placebo Composition 2	1 x Placebo Composition 3 and 1 x Test Composition 3
4. (Test composition 4)	1 x Placebo Composition 2	2 x Test Composition 3

Pain was assessed at baseline (0 hour), 0.25, 0.50. 0.75, 1.0, 1.25, 1.50, 1.75, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, and 24 hours after administration of study medication. Each patient individually determined and recorded time to perceptible pain relief and time to meaningful pain relief, using two stopwatches.

Time to onset of analgesia was then calculated for each patient by performing

a time-to-event analysis combining data from patient's stopwatch assessments of time to perceptible and meaningful pain relief. Baseline pain intensity for each group is shown in Table 11. Median time to onset of analgesia is shown in Table 12.

Table 11. Baseline pain intensity

Pain Scale	Test Composition 2	Test Composition 3	Test Composition 4
CPS		(%)	
Moderate	56	56	57
Severe	44	44	43
VAS		**0 to 100 mm**	
Mean	73.29	72.78	73.86

These data show that patients in each test group had comparable baseline pain intensity.

Table 12. Median time to onset of analgesia

Treatment	Time (min)
Placebo	>1440
Test Composition 2	31
Test Composition 3	28
Test Composition 4	31

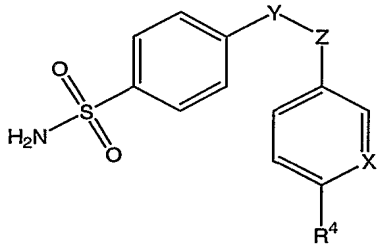
As determined in a similar pain study reported in International Patent Publication No. WO 01/91750, incorporated herein by reference, 200 mg Celebrex® capsules exhibit a median time to onset of analgesia of 41 minutes. The data in Table 12 show that patients taking Test Compositions 2, 3 or 4 experienced a relatively fast median time to onset of analgesia of 31 minutes or less.

WHAT IS CLAIMED IS:

1. An orally deliverable pharmaceutical composition comprising (a) a drug of low water solubility in a therapeutically and/or prophylactically effective amount and (b) a solvent liquid that comprises at least one pharmaceutically acceptable polyethylene glycol and at least one pharmaceutically acceptable free radical-scavenging antioxidant, wherein a substantial portion of the drug is in dissolved or solubilized form in the solvent liquid, and wherein the drug comprises an aminosulfonyl functional group and/or is capable of reacting with a polyethylene glycol or with a polyethylene glycol degradation product to form an addition compound.

2. The composition of Claim 1 wherein the drug is a selective cyclooxygenase-2 inhibitory drug.

3. The composition of Claim 2 wherein the selective cyclooxygenase-2 inhibitory drug is a compound of formula



where R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups.

4. The composition of Claim 3 wherein the five- to six-membered ring is selected from the group consisting of cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

5. The composition of Claim 2 wherein the drug is selected from the group consisting of celecoxib, deracoxib, valdecoxib and JTE-522.

6. The composition of Claim 2 wherein the drug is celecoxib.

7. The composition of Claim 2 wherein the drug is valdecoxib.

8. The composition of any of Claims 2 to 7 that further comprises a vasomodulator, wherein the selective cyclooxygenase-2 inhibitory drug and the vasomodulator are present in total and relative amounts effective to relieve pain in headache or migraine.

9. The composition of any of Claims 2 to 7 that further comprises an alkylxanthine compound, wherein the selective cyclooxygenase-2 inhibitory drug and the alkylxanthine compound are present in total and relative amounts effective to relieve pain in headache or migraine.

10. The composition of Claim 9 wherein the alkylxanthine compound is caffeine.

11. The composition of any of Claims 1 to 10 wherein the polyethylene glycol has an average molecular weight of about 100 to about 10,000.

12. The composition of any of Claims 1 to 10 wherein the polyethylene glycol is of liquid grade.

13. The composition of any of Claims 1 to 12 wherein the at least one free radical-scavenging antioxidant is present in the solvent liquid in a total amount of about 0.01% to about 5%, preferably about 0.01% to about 1%, by weight of the composition.

14. The composition of any of Claims 1 to 13 wherein the at least one free radical-scavenging antioxidant is selected from the group consisting of vitamin E, ascorbic acid and salts thereof, butylated hydroxyanisole, butylated hydroxytoluene, fumaric acid and salts thereof, hypophosphorous acid, malic acid, alkyl gallates, sodium thiosulfate, sodium sulfite, sodium bisulfite and sodium metabisulfite.

15. The composition of any of Claims 1 to 13 wherein the at least one free radical-scavenging antioxidant is an alkyl gallate, preferably propyl gallate.

16. The composition of any of Claims 1 to 13 wherein the at least one free radical-scavenging antioxidant is vitamin E.

17. The composition of any of Claims 1 to 16 wherein substantially all of the drug

present in the composition is in dissolved or solubilized form.

18. The composition of any of Claims 1 to 17 wherein the solvent liquid further comprises a turbidity-decreasing polymer.

19. The composition of Claim 18 wherein the at least one turbidity-decreasing polymer is hydroxypropylmethylcellulose.

20. The composition of any of Claims 1 to 19 wherein the solvent liquid further comprises at least one pharmaceutically acceptable fatty acid and at least one pharmaceutically acceptable organic amine.

21. The composition of Claim 20 wherein the at least one fatty acid is oleic acid.

22. The composition of Claim 20 or Claim 21 wherein the at least one organic amine is a tertiary amine selected from the group consisting of triethanolamine and dimethylaminoethanol.

23. The composition of any of Claims 1 to 22 that comprises one or more discrete dose units, wherein a therapeutically and/or prophylactically effective amount of the drug is contained in one to a small plurality of said dose units.

24. The composition of Claim 23 wherein each dose unit is a liquid-filled capsule having a capsule wall.

25. The composition of Claim 24 wherein the capsule wall comprises a turbidity-decreasing polymer.

26. The composition of Claim 25 wherein the turbidity-decreasing polymer is hydroxypropylmethylcellulose.

27. A method of treating a medical condition or disorder in a subject where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising orally administering to the subject a composition of any of Claims 2 to 10.

28. A method of analgesia comprising orally administering an effective pain-relieving amount of a composition of any of Claims 2 to 7 to a subject in need of analgesia.

29. The method of Claim 28 wherein the subject suffers from headache or migraine and wherein there is further orally administered to the subject a vasomodulator,

the selective cyclooxygenase-2 inhibitory drug and the vasomodulator being administered in total and relative amounts effective to relieve pain in the headache or migraine.

30. The method of Claim 28 wherein the subject suffers from headache or migraine and wherein there is further orally administered to the subject an alkylxanthine compound, the selective cyclooxygenase-2 inhibitory drug and the alkylxanthine compound being administered in total and relative amounts effective to relieve pain in the headache or migraine.

31. A method of use of a composition of any of Claims 2 to 7 in manufacture of a medicament useful for treating a medical condition or disorder in a subject where treatment with a cyclooxygenase-2 inhibitor is indicated.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 02/11690

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/415 A61K31/635 A61K47/48 A61K47/10 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 002 531 A (PANACEA BIOTEC LTD) 24 May 2000 (2000-05-24) page 2, line 9 - line 11 page 2, line 50 - line 56 examples 1,2 claims 9,10 ---	1-7, 11-14, 16,17, 27,28,31
A	US 5 552 160 A (LIVERSIDGE GARY G ET AL) 3 September 1996 (1996-09-03) abstract column 1, line 66 - line 67 column 2, line 35 - line 38 column 2, line 52 - line 54 column 3, line 29 column 3, line 42 --- -/--	1-7,11, 12,17

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 July 2002	01/08/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Hornich, E

INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 633 272 A (TALLEY JOHN J ET AL) 27 May 1997 (1997-05-27) the whole document	1-31
A	US 5 760 068 A (GRANETO MATTHEW J ET AL) 2 June 1998 (1998-06-02) the whole document	1-31
L	WO 01 91750 A (HASSAN FRED ;BRUGGER ANDREW (US); FORBES JIM (US); GAO PING (US);) 6 December 2001 (2001-12-06) abstract page 1, paragraph 2 page 7, paragraph 4 page 10, paragraph 2 page 14, paragraph 2 table 2 examples 3,4,6	1-6, 8-15, 17-31
L	WO 02 05799 A (HASSAN FRED ;FORBES JAMES C (US); PHARMACIA CORP (US)) 24 January 2002 (2002-01-24) page 6, line 24 -page 9, line 10 page 25, line 13 -page 27, line 12 page 40, line 6 -page 42, line 21 table 3 page 45, line 10 - line 14 page 47, line 3 - line 25 example 1; table 4 example 5; table 8 example 6; table 10 table 12	1-31
L	WO 01 78724 A (HASSAN FRED ;FORBES JAMES C (US); PHARMACIA CORP (US); HARIHARAN M) 25 October 2001 (2001-10-25) abstract page 6, line 16 -page 8, line 32 page 14, line 14 -page 15, line 31 page 24, line 18 - line 32 page 28, line 1 page 29, line 9 - line 18 page 32, line 7 claims in particular claims 9, 14-27	1-31

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 27-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The subject-matter of present claims 1 and 2 (and the claims dependent thereupon) is defined by means of functional features:

* '...wherein the drug comprises an aminosulfonyl functional group and/or is capable of reacting with a polyethylene glycol or with a polyethylene glycol degradation product ...'

* 'a selective cyclooxygenase-2 inhibitory drug'

Present claims 1 and 2 and the dependent claims 8-31) relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds defined by means of the Markush-formula given in claim 3 and the particular compounds defined in claim 5.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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